

# Salivary Cortisol Levels in Abused Children with Attention Deficit Hyperactivity Disorder

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## Abstract

**Introduction:** Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder during childhood. Family violence is a psychosocial factor that has been recently introduced in the literature about ADHD, with indications that parents of hyperactive children are more likely to use physical methods to their discipline. Cortisol as the primary stress hormone and as an index of the hypothalamic-pituitary-adrenal axis regulation has been used to study the neurobiological profile of ADHD patients.

**Methods:** This study was conducted on 50 ADHD children & 30 matched controls, severity was assessed using the Conners' Parent Rating Scales-Revised long version, children IQ and exposure to abuse was measured; salivary cortisol levels was measured using enzyme-linked immunosorbent assay in two samples (ELISA). Aim of the study was to measure prevalence and impact of abuse on ADHD children and correlate results with salivary cortisol level

**Results:** Results showed significant higher exposure of ADHD children to parental abuse than control group. Executive function showed to be impaired in abused ADHD children, lower bedtime cortisol level in abused ADHD children compared to control. There was a negative correlation between cortisol level and child abuse. In addition, there was a negative correlation between different types of abuse and components of WCST. While no correlation between both cortisol samples and components of WCST.

**Conclusion:** We concluded that children with ADHD displayed higher exposure to parental abuse, lower cognitive function and this was linked to their lower levels of cortisol level.

**Keywords:** ADHD; Cortisol; Executive function; Child abuse

## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder during childhood. It affects approximately 3–6% of school-aged children. The estimated prevalence of ADHD worldwide is 5.5% [1], and 7.48% in Egypt [2].

Family violence is a psychosocial factor that has been recently introduced in the literature about ADHD, with indications that parents of hyperactive children are more likely to use physical methods to their discipline [3]. Child abuse has been associated with a series of cognitive problems such as low academic performance and IQ, as well as specific deficits in language, memory, attention deficits and executive functions [4].

Childhood maltreatment is a severe stressor that, in addition to behavioral and cognitive problems, produces a cascade of physiological, neurochemical, and hormonal changes, which can lead to enduring alterations in brain structure and brain function [5]. The hypothalamic-pituitary-adrenal (HPA) axis represents one of the body's core stress response systems. It is established that the physiological response to stress, as indicated by levels of cortisol, is related to distinct aspects of cognition, including declarative memory as well as executive functions. When stressful conditions are chronic or persistent, stress response systems are said to be under high allostatic load and adapt to the environment with over or under activation to an extent that impedes flexible regulation of cortisol, such as that associated with the self-regulation of behavior and executive functions [6].

The present study aimed at comparing salivary cortisol levels and executive functions measured by Wisconsin card sorting test (WCST) between ADHD and matched controls; and investigating the impact of

child abuse on salivary cortisol levels and executive functions in ADHD children.

## Materials and Methods

A cross-sectional pilot study was conducted at the outpatient of Child and Adolescent Clinic of Institute of Psychiatry of Ain Shams University hospitals and Children with special needs clinic, National Research Centre, Egypt.

The study included 50 ADHD patients diagnosed according to DSM-IV-TR criteria [7], and thirty healthy; age, sex, IQ, socioeconomic level matched children served as controls. Informed written consent was obtained from the controls and parents/ guardians of ADHD children. The study protocol was approved by Institutional Ethical Committees of the National Research Centre, Giza, Egypt. Participants with an IQ score below 85 or pervasive developmental disorder, history of neurological or chronic medical conditions, or any hormonal treatment were excluded from the study.

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All participants were subjected to the following:

1. Full medical history and thorough clinical examination to rule out any infectious or physical diseases present.
2. Clinical psychiatric interview by The Mini-International Neuropsychiatric Interview for Children / adolescents (MINI-Kid) to confirm diagnosis and exclude co- morbidity. MINI-Kid is a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders [8], using Arabic version translated into Arabic language and had the reliability and validity tests done by Ghanem et al., [9].
3. Intelligent quotient (IQ) testing Arabic version [10] the test is designed to measure human intelligence as reflected in both verbal and nonverbal (performance) abilities.
4. The Conners' Parent Rating Scales-Revised Long version (CPRS-R-L) for assessing ADHD symptoms [11].
5. Child abuse and neglect scale for children [12]. This scale has been developed after considering of other child abuse and negligence scales and collection of observations about the causes of child abuse from different foreign and Arabic studies and showed high reliability and validity. It is formed of three sub-scales: physical abuse, emotional abuse and neglect scale. Each sub-scale consists of (22) items. The total score of the scale lies in three levels: (zero-66) means low or mild degree of child abuse, (67-132) moderate abuse, (133-198) and severe abuse.
6. The Computerized Wisconsin Card Sorting Test (WCST) for evaluating the executive performance [13].
7. Estimation of salivary cortisol levels using enzyme- linked immunosorbent assay (ELISA) kit supplied by DRG Instruments GmbH, Germany in two samples (morning and bedtime) were done [14].

### Sample collection

Sampling was performed at home by the participants. The morning sample was collected within a half-hour of waking and the night sample was collected within a half-hour of bedtime to assess circadian rhythm. Instructions were given that the sampling should be done before brushing teeth, at least 30 min after eating or drinking and at least 1 h after sport activity. If there was visible blood contaminating the specimen, it must be discarded, the mouth rinsed then new sample can be taken after 10 min. Samples was collected by swabs (Salivette; Sarstedt Inc., Rommelsdorf, Germany), the participants keep it in their mouth 1-2 min until soaked with saliva. The swabs were placed in plastic sampling tubes. The tubes were centrifuged and stored at -20°C until analyzed.

### Statistical analysis

Variables are expressed as mean and Standard Deviation. Categorical variables are expressed as frequencies and percents. Student t test and ANOVA test was used to assess the statistical significance of the difference between two and more than two study groups means respectively. Chi Square and Fisher's exact test were used to examine the relationship between Categorical variables. Pearson's correlation was used to assess the correlation between quantitative variables. Multivariate Linear regression was used to test and estimate the dependence of a quantitative variable based on its relationship with a set of independent variables. A P value less than 0.05 was considered statistically significant. Calculations of data were done on SPSS v.15 (SPSS incorporation, Chicago, Illinois).

### Results

Fifty Attention deficit Hyperactive disorder (ADHD) cases were included in this study, 27 males and 23 females with their mean age was  $11.024 \pm 1.351$  years. They were sub grouped according to abuse scale scoring into 2 groups; 28 abused ADHD patients and 22 non-abused ADHD patients. Occurrence of abuse was operationally defined in the studied sample as children scoring more than 66 on the child abuse and neglect scale for children. From 0 to 66 was deemed no abuse (minimal occurrence of the abuse).

Statistical analysis of the results showed that ADHD cases showed statistically significant higher exposure to different types of abuse from both parents than controls ( $p < 0.001$ ). Fathers were significantly higher abuser than mothers in all types of abuse (Table 1).

Evaluating the executive functions by WCST revealed that ADHD cases performed significantly worse than controls in all items except preservation errors test (Table 2).

Comparing salivary cortisol at morning and bedtime, bedtime samples of ADHD cases were significantly lower than controls with no statistical difference was found at morning sample (Table 3).

These findings were further confirmed by correlation studies, where a negative correlation between cortisol level (both at morning and bedtime), and parental abuse was evident, negative correlation between different types of parental abuse and components of WCST, while no correlation between cortisol levels and WCST (Tables 4 and 5).

### Comparison of the 2 ADHD subgroups and controls

ADHD-abused had lower performance in WCST when compared with ADHD-non abused & control group (Table 6).

Comparing salivary cortisol level revealed that abused ADHD cases had the lowest mean in both morning and bedtime samples among 3 groups, and a high statistical difference between abused and non-abused ADHD cases in night samples (Table 7).

### Discussion

In the present study ADHD children were exposed to higher degrees of abuse than controls. Psychological followed by physical abuse were the most frequent type of abuse practised by both parents while negligence was less frequent to occur. These results agreed with a previous study was done in Iran, it showed that parents of children with ADHD used corporal violence more commonly than parents of children without the disorder [15]. In a study with 14,322 North-American children who were followed longitudinally, the results showed: physical, sexual violence and negligence practiced by the parents against their children were related to the highest prevalence of ADHD [16]. The children with ADHD and disruptive behavior had three times higher odds of having suffered physical abuse [17], we found out that fathers were more abusing than mothers in abused ADHD group regarding different types of abuse with high statistical difference, this finding is consistent with Alizadeh et al., who reported that parent's gender predicts parenting styles, and that mothers are generally more authoritative, whereas fathers are more authoritarian. On the other hand, dissimilarity of parenting styles within a family is related to higher parenting stress [18].

When testing subjects using the Wisconsin Card Sorting Test (WCST), children with ADHD performed more trials to be able to finish the test, showed more errors, could not reach the first sorting principle after the same number of trials as control children, showed

		Father Mean ± SD	Mother Mean ± SD	t	p-value
Physical	Abused ADHD	48.18 ± 11.48	30.68 ± 11.72	5.162	<0.001*
	Non-abused ADHD	18.23 ± 9.07	14.96 ± 9.31	1.717	0.101
	Controls	10.03 ± 7.11	7.57 ± 8.76	1.219	0.233
Psychological	Abused ADHD	51.61 ± 9.64	38.21 ± 10.79	5.613	<0.001*
	Non-abused ADHD	21.18 ± 7.94	18.73 ± 10.83	1.021	0.319
	Controls	13.20 ± 7.99	11.30 ± 6.62	1.216	0.234
Negligence	Abused ADHD	43.11 ± 13.35	35.18 ± 14.10	2.301	0.029*
	Non-abused ADHD	16.73 ± 7.01	16.82 ± 11.01	-0.037	0.971
	Controls	10.87 ± 8.46	9.00 ± 6.09	1.001	0.325
Total	Abused ADHD	142.89 ± 26.59	103.64 ± 24.53	5.568	<0.001*
	Non-abused ADHD	52.23 ± 13.15	45.96 ± 17.87	1.614	0.122
	Controls	34.10 ± 20.32	27.93 ± 18.31	1.342	0.19

\*p value significant

Table 1: Comparison between father and mother abuse among different groups.

	ADHD cases		Controls		p	Sig.
	Mean	± SD	Mean	± SD		
IQ	97.04	8.607	100.4	7.828	0.084	NS
Perseverative errors	27.02 ±	11.68	12.17	6.71	<0.001*	HS
Non- perseverative errors	22.72	8.38	9.3	4.6	<0.001*	HS
Number of categories completed	3.62	1.35	5.5	0.57	<0.001*	HS
Conceptual-level responses	59.4	18.67	76.43	10.28	<0.001*	HS
Trials to complete first category	18.28	7.5	14.37	2.89	0.008*	HS
Failure to maintain a set	2	1.134	0.77	0.89	<0.001*	HS

Table 2: Comparison between cases and controls as regards IQ and WCST.

more perseveration responses whether correct or incorrect even when a feedback was given, were less successful in completing a set of five or more correct consecutive matches and completed less number of test categories. These findings are explained by Hybrid Neuropsychological Model of Executive Functions & Extension of the Model to ADHD that states that the deficiency in behavioral inhibition that characterizes ADHD diminishes the effective deployment of the executive abilities that subserve self-control and goal-directed behaviour. The stopping of an on-going response pattern is required in the performance of WCST [19].

In keeping with this interpretation, three meta-analyses computed small (0.35) to medium (0.52) effect sizes for the differences in mean perseverative errors between ADHD individuals and non-ADHD controls on the WCST [20-22]. ADHD individuals made more perseverative errors on the WCST than did non-ADHD controls, suggesting that ADHD is associated with impaired cognitive flexibility.

In a recent study that examined different neuropsychological

Salivary Cortisol (ng/mL)	ADHD Cases Mean ± S.D	Controls Mean ± S.D	t	p
Awakening	10.17 ± 7.35	13.97 ± 12.76	-1.691	0.095
Bedtime	3.9 ± 2.4	5.46 ± 3.19	-2.482	0.015*

Table 3: Comparison between cases and controls as regards salivary cortisol level in two samples.

	Cortisol level at awakening		Cortisol level at bedtime	
	r	p	r	p
Father (total score)	0.165	0.253	-0.275	0.053
Father (physical abuse)	-0.46	0.001*	-0.13	0.367
Father abuse (psychological abuse)	-0.341	0.015*	-0.332	0.018*
Father (neglect)	-0.299	0.035*	-0.155	0.283
Mother (total score)	-0.423	0.002*	-0.382	0.006*
Mother (physical abuse)	-0.328	0.020*	-0.175	0.223
Mother (psychological abuse)	-0.012	0.936	-0.306	0.031*
Mother (neglect)	-0.294	0.038*	-0.257	0.071

Table 4: Correlation of cortisol level at awakening and bedtime with Child abuse and negligence rating scale in ADHD cases.

	Cortisol level at awakening		Cortisol level at bedtime	
	r	p	r	p
IQ	0.271	0.057	0.12	0.408
Perseverative errors	-0.153	0.288	-0.124	0.393
Non- perseverative errors	-0.055	0.702	-0.059	0.682
Number of categories Completed	0.11	0.446	0.127	0.38
Conceptual-level responses	0.232	0.105	0.267	0.061
Trials to complete first Category	-0.246	0.086	-0.059	0.685
Failure to maintain a set	0.045	0.761	-0.161	0.268

Table 5: Correlation between cortisol level at awakening and bedtime, IQ and WCST in ADHD cases.

domains: executive functions (working memory, inhibition, and shifting), delay aversion, and reaction time variability, children with ADHD differed significantly from controls on all measures, except for delay aversion and recognition of disgust [23].

On the other hand, the meta-analysis conducted by Walshaw et al., groups with ADHD exhibited significant impairment on all EF tasks [24]. Effect sizes for all measures fell in the small to medium range, but the strongest and most consistent effects were obtained on measures of response inhibition, vigilance, working memory, and planning. They argued that small- moderate effect sizes and lack of universality of EF deficits among individuals with ADHD suggest that EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD. In a study investigated the relationship between EF, ADHD subtypes, and comorbid diagnosis by taking into account the potential role of IQ, Co morbidity patterns, rather than ADHD subtypes, appear to be more valid for defining the neuropsychological features of the ADHD endophenotype.

	Abused ADHD cases	Non-abused ADHD cases	Controls
Perseverative errors	31.68 ± 11.91	21.09 ± 8.38	12.17 ± 6.71
	P <sub>1</sub> <0.001*	P <sub>2</sub> <0.001*	P <sub>3</sub> =0.003*
Non- perseverative errors	24.034 ± 7.51	21.05 ± 9.29	9.3 ± 4.61
	P <sub>1</sub> =0.313	P <sub>2</sub> <0.001**	P <sub>3</sub> <0.001*
Number of categories Completed	2.93 ± 1.27	4.5 ± 0.856	5.5 ± 0.58
	P <sub>1</sub> <0.001*	P <sub>2</sub> <0.001**	P <sub>3</sub> =0.001*
Conceptual-level responses	52.29 ± 18.76	68.45 ± 14.39	76.43 ± 10.28
	P <sub>1</sub> = 0.001*	P <sub>2</sub> <0.001**	P <sub>3</sub> =0.141
Trials to complete first Category	19.18 ± 8.69	17.14 ± 5.64	14.37 ± 2.89
	P <sub>1</sub> =0.482	P <sub>2</sub> =0.011*	P <sub>3</sub> =0.254
Failure to maintain a set	2.08 ± 1.19	1.91 ± 1.09	0.77 ± 0.89
	P <sub>1</sub> =0.849	P <sub>2</sub> <0.001**	P <sub>3</sub> =0.001*

P<sub>1</sub>: Abused ADHD vs. non- abused ADHD; P<sub>2</sub>: Abused ADHD vs. controls; P<sub>3</sub>: Non-abused ADHD vs. controls

**Table 6:** Comparison between 2 ADHD groups and controls as regard WCST.

	Abused ADHD	Non- abused ADHD	Controls	F	p-value
Awakening (ng/ mL)	7.53 ± 3.9	13.54 ± 9.22	13.97 ± 12.7	3.982	0.023*
	P <sub>1</sub> = 0.073	P <sub>2</sub> =0.031*	P <sub>3</sub> =0.986		
Bedtime (ng/mL)	3.03 ± 1.67	5.01 ± 2.78	5.46 ± 3.19	6.817	0.002*
	P <sub>1</sub> =0.026*	P <sub>2</sub> =0.002*	P <sub>3</sub> =0.812		

\*p < 0.05 =significant

P<sub>1</sub>: Abused ADHD vs. non- abused ADHD; P<sub>2</sub>: Abused ADHD vs. controls; P<sub>3</sub>: Non-abused ADHD vs. Controls

**Table 7:** Comparison between ADHD groups and controls as regards salivary cortisol level on all sampling occasions.

The nature of the neuropsychological deficits in ADHD remains elusive and findings are heterogeneous. Methodological differences, such as the criteria used to select the studied populations, different measures of EF and comorbidity could explain the controversial findings reported in neuropsychological articles [25].

Comparing the performance in WCST and ADHD groups, our results showed that: Abused ADHD children committed significantly more perseverative errors, showed more perseveration responses whether correct or incorrect even when a feedback was given than non- abused ADHD and achieved fewer categories but there was no statistically significant difference between them regarding non-preservative errors, trials to complete first category and success in completing a set of five or more correct consecutive matches. There was a positive correlation between different types of abuse by both parents is associated with most of the executive functions tapped by the WCST. Consistent with these studies, Kirke-Smith et al., [26] reported that maltreated adolescents (with history of childhood trauma) had significantly lower performance than non-maltreated adolescents on tasks assessing executive functions. The inclusion of emotional and behavioural difficulties had some effect on group differences but did not eliminate them. While Augusti and Melinder, [27] observed that maltreated children performed significantly poorer compared to their non-maltreated peers on the spatial working memory task.

Comparing salivary cortisol levels at morning and at bedtime

(diurnal pattern) between ADHD cases and controls showed no statistical difference in morning level. On the other hand, the cortisol levels in night samples of ADHD cases were lower than controls. Comparing the 3 groups showed that abused ADHD cases had lower cortisol levels in morning and night than non-abused ADHD and controls, and no statistical difference between non-abused ADHD and controls in both samples. These findings were confirmed by the correlation studies, cortisol levels in both samples showed negative correlation with most types of abuse practiced by both parents meaning that exposure to psychosocial adversity explained and changed the strength of the relationship between ADHD-symptoms and cortisol levels.

Most studies of diurnal patterns of cortisol reported a relationship between ADHD symptoms and altered circadian cortisol patterns [28]. Results are inconsistent however showing both hypo and hyper arousal deviations at different time points. Considering studies with repeated measurements across 1 day [29] originally found a normal diurnal cortisol pattern in only 43.3% of the children with ADHD, suggesting a dysregulation of the HPA axis in the majority of children. Ma et al., [30] found a lower cortisol awakening response in a group of children with ADHD compared to a group of controls. The main findings of Isaksson et al., [5] were that children with ADHD had significantly lower salivary cortisol levels in the morning and evening than non-affected comparisons. Two studies did not find any difference on morning cortisol between children with ADHD (without comorbid disorders) and control children [31].

There was no correlation between both cortisol samples; and IQ and components of WCST was found except for positive significant correlation between cortisol at bedtime and learning to learn score ( $p=0.034$ ), weak positive correlation near to statistical significant difference between cortisol at waking and IQ ( $p=0.057$ ), and between cortisol at bedtime and conceptual-level responses ( $p=0.061$ ) which means that cortisol was associated weakly with cognition but did not mediate the impact of exposure to abuse on executive functions. Cicchetti et al., [32] reported in a sample of maltreated children that low basal levels of cortisol were associated with impairments in false recognition memory in neglected/emotionally maltreated children, while Blair et al., [33] reported that salivary cortisol mediated the effect of negative parenting on working memory and attention shifting domains of executive functions in a large young-aged population followed longitudinally with cortisol measured 3 times with a 6 months interval. Despite several studies with adults, few studies have examined relations between cortisol and children's cognitive performance. Existing evidence is mixed with some reports of no significant relations [34]. Other studies documented that higher morning cortisol levels are associated with worse performance on a memory speed task [35], and greater cortisol reactivity is correlated with academic difficulties and attention problems in a sample of 5- to 12-year-olds [36]. In a sample of 6 to 16 year old children, differences in basal cortisol levels were not related to cognitive functioning [37].

An explanation to discrepancy in these findings is that saliva sampling was performed during one regular weekday, limited to two occasions. For optimal cortisol measurement, it is advisable to collect saliva for more than 1 day also assessing participant's adherence [38]. However; we wanted the sampling to be done on a regular day since the day of cortisol assessment is crucial in psycho-endocrinological stress studies. We also assumed that the procedure with numerous collecting points would be too demanding and might increase attrition. Another possible explanation is the methodological differences in assessing

cognitive and executive functions association with cortisol in different studies; cortisol might be linked to domains of executive functions (other than set shifting) that were not assessed in this study.

## Conclusions

We concluded that children with ADHD displayed lower levels of cortisol and executive dysfunction. These findings were linked to early exposure to abuse from parents, focusing on the impact of child maltreatment on proper functioning of ADHD child. It is important for pediatricians and other health care providers to be aware of the link between child maltreatment and psychiatric disorders, which adds to the growing literature about the adverse outcomes associated with exposure to abuse. In clinical settings, we recommend examining both the fathers' and mothers' parenting styles in dealing with their children. In making such a recommendation, it will be important to provide information about alternative discipline strategies, such as positive reinforcement and rewards. However, further studies are needed in a larger cohort and different socio-economic levels to confirm impact of abuse on ADHD children.

## Strengths and Limitations

This study has highlighted the accumulating evidence pointing to a variety of neurobiological changes associated with child abuse attempting to demonstrate the link between biological factors and psycho-social stressors; and their impact on cognitive abilities in ADHD children. Developmental neuroscience research is just one small part of a wider societal endeavor to better understand the complex repercussions of child maltreatment, so that as clinicians working with children with ADHD become better at early intervention and prevention.

The saliva sampling was performed during one regular weekday, limited to two occasions. For optimal cortisol measurement, it is advisable to collect saliva for more than 1 day also assessing participant's adherence. However, we wanted the sampling to be done on a regular day since the day of cortisol assessment is crucial in psycho-endocrinological stress studies. We also assumed that the procedure with numerous collecting points would be too demanding and might increase attrition.

## Ethical Approval

Approval to conduct this study was granted by the Ethical Committee of the National Research Centre and Ethical committee of Institute of Postgraduate Childhood Studies Ain Shams University

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## Conflict of interests

No conflict of interest to declare

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