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Hypothalamic-Pituitary-Adrenal Reactivity in Boys with Attention Deficit Hyperactivity Disorder

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The hypothesis 'whether subjects with attention-deficit/hyperactivity disorder (ADHD), who showed under-reactivity of the hypothalamic-pituitary-adrenal (HPA) axis to stress, would make more commission errors in attention tasks', was examined. Forty-three boys, with ADHD, who visited the psychiatric outpatient clinic, at Kangbuk Samsung Hospital, were the subjects of this study. Both pre- and post-test morning saliva samples were collected from the patients at the Korean Educational Development Institute-Wechsler Intelligence Scale for Children (KEDI-WISC), and Tests of Variables of Attention (T.O.V.A.) performed. The Standard scores of the T.O.V.A were compared between the patients with decreases, or increases, in the salivary cortisol levels after the test. Decreases, or increases in the salivary cortisol levels after the test were shown in 28 and 15 patients, respectively. The patients with decreased cortisol levels after the test tended to make more commission errors in compared with those with increased cortisol levels. The patients with the decreased cortisol levels after test had more omission errors in the first quarter of the test, and more commission errors in the second half of the test compared to those with the increased cotisol levels. Subjects who show decreased salivary cortisol levels after stress make more commission errors in attention tests. This suggests that the blunted HPA axis response to stress is related to the impulsivity in patients with ADHD.

Key Words: ADHD, HPA axis reactivity, impulsivity

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by inattention, hyperactivity, and impulsivity.[1] About 30% of the symptoms persist into adulthood.[2] ADHD is accompanied by academic under-achievement, substance abuse, conduct problems, anxiety, depression, marital problems, and occupational adjustment.[3] Although ADHD is a commonly observed disorder, with many accompanying problems, the core pathology underpinning the disorder still remains to be clearly understood. This may be the reason why many researchers have shown interested in scrutinizing the ADHD.[4]

Recently, some theorists have argued that a poor response inhibition is the central feature of ADHD.[5-7] They insist that dysfunction of the behavior inhibition system (BIS) has major roles in the mechanism of ADHD. Dysfunction of the behavior inhibition system results in secondary deficits of working memory, self regulation of affect, internalzation of speech and reconstitution like goal-directed behavior. These secondary deficits are related to a decrease in the controlling of the motor function monitored by internally represented information. A poor response inhibition, related to dysfunctional executive function, leads to problems of self-control and goal-directed behavior.[5] The view concerning the poor response inhibition in ADHD seems to have some benefits in explaining the abnormal findings of the prefrontal functioning of patients with ADHD.[8] The concept of behavior inhibition has been adapted from Gray's psychological theory on anxiety disorders.[9] Signals of punishment, and frustrative non-reward, activates the monoaminergically mediated behavior inhibition system.

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This activation results in endocrinological responses, including elevation of the level of cortisol.[10] If one of the core deficits of the ADHD is the dysfunctional behavior inhibition system, abnormality in HPA axis reactivity should be observed in patients with ADHD. It was reported that urinary excretion of the epinephrine, during intelligence tests is at least 40% lower in patients with ADHD than in control subjects. Under-reactivity of the hypothalamic-pituitary-adrenal (HPA) axis to stress in patients with ADHD has been reported to be related with their poorer performance.[11] The cortisol levels of patients with ADHD, who retained their diagnosis for more than 1 year, were compared with those that did not. The subjects with ADHD, who retained their diagnosis over the first year of the study, showed a blunted response to the stress compared to those that no longer retained the disorder. An impaired response to stress might be a marker for the more developmentally persistent form of the disorder.[12] This finding suggests that only a portion of the patients with ADHD have a dysfunctional HPA axis reactivity, and this abnormality is related to the persistence of the disorder.

Although previous studies reported that some patients with ADHD have a dysfunctional HPA axis reactivity,[11,12] few studies have designed to compared the difference between the patients with a blunted response and those who retain the normal response to stress. As the under-reactivity of the HPA axis has been reported to be related to impulsivity,[13-15] it was expect that patients with under-reactivity of the HPA axis would show more impulsivity. The hypothesis- 'whether subjects with ADHD, who showed under-reactivity of the HPA axis to stress, would make more commission errors in continuous performance tests, and show a negative correlation between the cortisol decrement and the level of performance measured by continuous performance tests'.

MATERIALS AND METHODS

Subjects

Forty-three boys with ADHD, recruited from the psychiatric outpatient's clinic, at Kangbuk Samsung Hospital, were the subjects of this study. Two child psychiatrists made the diagnoses of ADHD using the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV).[1] Parents and teachers completed a Conners Parent-Teacher Questionnaire (CPTQ). All the patients got scores 15 points higher than those of the parents and teachers.[16] The patients with a comorbid diagnosis, including patients with IQ score lower than 75, by the Korean Educational Development Institute-Wechsler Intelligence Scale for Children (KEDI-WISC), were excluded. Those patients with a comorbid diagnosis, other than ADHD, using the DSM-IV diagnostic criteria, were also excluded. No subjects had a history of stimulant medication administration. The written informed consents of the patients and parents were obtained after explaining the purpose and course of the study.

Test of variables of attention (T.O.V.A.)

The T.O.V.A. is a computerized continuous performance test. It is a reliable test for the diagnosis and evaluation of the effect of treatments for ADHD.[17] Patients are asked to push a button, connected to a computer, when they recognized the target on the monitor. The target refers a small square appearing in the upper part of a rectangle. A small square appearing at the bottom of the rectangle is considered to be a non-target. One of these to stimuli would flash on the screen every two seconds. The two targets are presented on 22.5% and 77.5% of the trials during the first and second halves, respectively. Data are obtained in domains of omission error, commission error, response time, and variability. When the subjects failed to respond to the target stimuli, their omission error scores will decrease, which reflects the inattention. The commission error scores decreases when subjects respond to the non-target stimuli, which reflects the impulsivity. Lower scores are a sign of poorer performance in the attention tasks.[15] All variables are recorded for each 5-min quarter and 10-min half, as well as for the overall total scores for each variable. Scores are compared to standardized norms, and an interpretation of data reported in a printable form.

Cortisol determinations in saliva

All the samples for the baseline measurements of the cortisol level were collected between 10:30 and 11:00 a.m. All patients took 30 minutes rest prior to the saliva sample collection. Fifteen minutes before the KEDI-WISC and Test of Variables of Attention (T.O.V.A.)[17] had been performed, mouth was rinsed thoroughly with water, and patient was asked to chew sugarless gum, to stimulate the secretion of saliva. Saliva samples were collected for the analysis of the pre-test cortisol level. 20 cc saliva samples were collected in plastic containers.

Thirty minutes after the tests, the patient's mouth was rinsed thoroughly with water. Sugarless gum was chewed and saliva was collected. The specimen frozen to precipitate the mucin., after thawing, the sample was centrifuged, and the supernatant transferred to a clean container. Materials supplied in Diagnostic Products Corporation's Coat-A-Count Cortisol kit (Los Angeles, CA, USA) were used to measure the level of saliva cortisol. Four uncoated tubes were labeled as T for total counts and as NSB for nonspecific binding in duplicate. Twelve cortisol antibody coated tubes were labeled as A for maximum binding and B through F in duplicate for controls and patient samples. Each calibrator and serum-based control was diluted 1-in-10 in water and mixed by gentle vortexing. 200 μL of the diluted calibrator A was pipetted into the NSB and A tubes, 200 μL of each remaining diluted calibrator and control, and 200 μL of each undiluted saliva sample were pipetted into the tubes prepared. 1.0 mL of [^{123}I] cortisol was added to every tube. After vortexing, tubes were incubated for 3 hours at room temperature. Samples were decanted thoroughly, and counted for 1 minute in a gamma counter.

Statistics

On the basis of the HPA axis reactivity, the patients with ADHD were divided into two groups. Group 1 consisted of the patients that showed decreased cortisol levels, and group 2 of those that showed increased cortisol levels after the test. A paired t-test was used to compare the pre- and post-test means cortisol levels between the two groups. The difference between pre- and post-test cortisol levels were computed for each group, and the absolute mean values of the differences were compared using the Student's t-test. The standard T.O.V.A. scores between the groups were also compared using the Student's t-test. A Pearson's correlation analysis was used to examine the correlation between the cortisol levels after the test and the standard T.O.V.A. scores.

RESULTS

Of the forty-three patients, 28 showed a decrease, and 15 an increase, in the salivary cortisol levels after the test, (groups 1 and 2), respectively. There was no significant difference in ages and intelligence scores between these two groups (Table 1).

In each group, the salivary cortisol levels showed significant change from the baseline (group 1, t= 7.160, df=27, $p<0.01$; group 2, t=-2.712, df=14, $p<0.05$), but the absolute values of the differences were not significantly different between the two groups (Fig. 1).

Table 2 summarizes the T.O.V.A. test results. Group 1 showed a tendency to have lower com-

Table 1. Age and Scores of Intelligence Test of Patients with Attention Deficit Hyperactivity Disorder

	Group 1 (N=28)	Group 2 (N=15)
Age	10.6 ± 1.7	10.0 ± 2.1
Verbal IQ	103.3 ± 13.9	105.0 ± 14.7
Performance IQ	103.7 ± 13.4	97.9 ± 18.2
Total IQ	103.9 ± 14.2	102.0 ± 17.2

Group 1, patients with decreased post-test cortisol level.
Group 2, patients with increased post-test cortisol level.

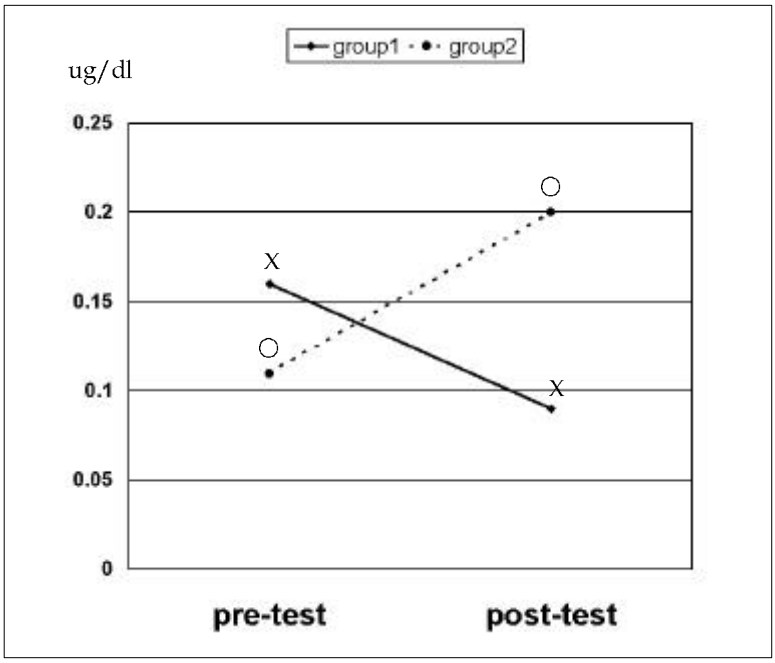

Fig. 1. Pre-test and post-test cortisol level. Group 1: patients with decreased post-test cortisol level. Group 2: patients with increased post-test cortisol level. X $p<0.01$; ○ $p<0.05$.

Table 2. Standard Scores of T.O.V.A.

	Group 1 (mean ± SD)	Group 2 (mean ± SD)	p Value
OQ 1	94.1 ± 17.3	103.3 ± 5.0	0.016*
OQ2	100.0 ± 12.95	97.3 ± 10.9	0.5232
OQ3	94.7 ± 19.9	99.1 ± 7.2	0.448
OQ4	91.1 ± 20.0	90.1 ± 20.0	0.875
CQ1	96.1 ± 19.3	103.7 ± 7.2	0.176
CQ2	90.3 ± 22.3	103.7 ± 7.24	0.008†
CQ3	98.7 ± 22.1	99.7 ± 16.0	0.882
CQ4	104.2 ± 18.7	105.6 ± 15.0	0.807
RQ1	96.1 ± 17.6	90.3 ± 16.8	0.333
RQ2	96.7 ± 19.6	92.7 ± 17.6	0.536
RQ3	95.7 ± 17.3	92.0 ± 18.5	0.539
RQ4	93.5 ± 17.2	87.2 ± 24.1	0.350
VQ1	95.0 ± 18.0	96.5 ± 15.1	0.792
VQ2	93.5 ± 18.8	98.6 ± 15.5	0.404
VQ3	92.7 ± 21.1	99.0 ± 14.2	0.339
VQ4	95.0 ± 18.4	93.0 ± 16.7	0.748
O	94.4 ± 15.3	97.0 ± 8.9	0.570
C	100.0 ± 19.8	104.3 ± 11.0	0.468
R	94.3 ± 17.87	88.4 ± 22.6	0.379
V	93.5 ± 18.7	95.1 ± 17.0	0.791

Group 1, patients with decreased post-test cortisol level.
Group 2, patients with increased post-test cortisol level.
Q1, first quarter of total test time; Q2, second quarter of total test time; Q3, third quarter of total test time; Q4, fourth quarter of total test time; O, omission error; C, commission error; R, response time; V, variability.

*$p<0.05$.
†$p<0.01$.

mission error scores. In the domains of the omission and commission errors, the subjects in the group 1 committed significantly more errors in the first and second quarters of the test, respectively(t=-2.537, df=33.6, $p<0.05$), and (t=-2.830, df= 34.981, $p<0.01$) compared to subjects in the group 2.

A significant correlation was observed by subtracting the pre- from the post-test cortisol levelsand the scores for the response time in group 1 (r=0.454, $p<0.05$). A significant negative correlation was obtained by subtracting the pre- from the post-test cortisol levels and the commission error scores in group 2 (r=-0.625, $p<0.05$).

DISCUSSION

The most salient physiological responses to stress are increased by norepinephrine (NE) and cortisol.[18-20] Since the level of the saliva correlates well with the level of serum cortisol, saliva cortisol has been used to evaluate the reactivity of the HPA axis.[21,22] Measurements of the saliva cortisol levels are particularly useful in the study of children's reactivity to stress,[23-25] as collecting the saliva samples is less invasive and accompanied by less stress.

Patients with ADHD show decreases in the urinary epinephrine output during intelligence testing, while normal controls show increases.[11] Comorbid patients, with ADHD and oppositional-defiant disorder, receiving no stimulant medication show lower level of saliva cortisol than normal controls.[14] These endocrine findings support the view that a poor response inhibition is one of the core features of ADHD.

In patients with ADHD 43.3 and 46.7% showed an abnormal diurnal variation in the cortisol levels, and had abnormality in dexamethasone suppression tests, respectively. These findings are more evident in patients with hyperactivity.[26] Some patients with ADHD, who retained their diagnosis more than 1 year, showed a blunted response to stress, but the cortisol level increased after stress in the patients who did not retain their diagnosis for more than 1-year. The reactivity of the HPA axis to stress may have prognostic significance.[12] These findings assist in the speculation that not all patients with ADHD have an underreactivity of the HPA axis, and those that do may have more deficits than the patients with an appropriate reactivity. Few studies have demonstrated the impulsivity associated with the dysfunctional reactivity of the HPA axis to stress in ADHD. In the present study, more commission errors tended to be observed in the patients with a decrease in the cortisol levels after the test. In the second quarter of the total test time, the difference in the commission errors between the patients with a decrease and an increase in the cortisol levels after the test reached statistical significance. This result is consistent with the hypothesis that low reactivity of cortisol is related to impulsivity. Linked with previous reports,[12] it is proposed that of the patients with ADHD, some that have a dysfunctional HPA axis reactivity will retain their symptoms for longer than those with a normal HPA axis reactivity, and therefore show more impulsivity.

It has been reported that a lower urinary free cortisol level during continuous performance tests was correlated with a shorter reaction time in disruptive boys.[27] The result of the present study is consistent with this finding. The more the cortisol levels were decreased after stress, the shorter the response time. This possibly reflects that low levels of cortisol shorten the response time.

In the present study, it was observed that some of the patients with ADHD maintained their reactivity to stress. In this group of patients, the cortisol levels were negatively correlated with the omission error score in the attention test. The more the cortisol levels were increased after stress, the more omission errors were evident. The findings from the normal controls have shown an inverted U shape relationship between the cortisol and performance levels for the attention tasks.[28] Too much cortisol has a negative influence on the level of performance, which was in accord with the findings in this study.

One of the limitations of this study was the small sample size. To compensate for this, a Levene's test for equality of variances was used, and an appropriate P value adopted. However, this study, only the second quarter of the commission errors reached significance. If the sample

size had been larger, more scores from other quarters may have reached significance. Further investigations should be carried out with larger samples.

Our diagnoses were not made with the use of structured or semi-structured interview toolt. To compensate for this, only the patients that met the DSM-IV diagnostic criteria for ADHD, and who achieved a score 15 points higher in the CPTQ than those of the parents and teachers, were included. A score of 15 points, or more, plus 2 standard deviation in the CPTQ has been used as the mean cut off point.

In this study, two distinct patient groups with ADHD were identified according to the reactivity of the HPA axis to stress. Some of the patients showed a decrease in the cortisol levels after stress, and others an increase.

This finding provides evidence of the feasibility of the reactivity of the HPA axis to stress as a possible marker for defining subgroups of patients with ADHD. The heterogeneity of ADHD is a crucial issue in genetic research fields.[29] The major reason for the inconsistent findings in association studies of ADHD is believed to be the heterogeneity of this disorder.[30,31] An endophenotypic measurement has been suggested as a useful tool to overcome this problem.[32] Our findings indicate that the reactivity of the HPA axis could possibly be used as an endophenotypic measurement. Further studies on the recognition of the characteristics of patients with ADHD, with a dysfunctional HPA axis reactivity, are expected.

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