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Stress in Children with Pervasive Developmental Disorders

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SUMMARY

The purpose of this study is to examine urinary 17-hydroxycorticosteroid (OHCS) excretion as a measure of stress response in controls and in children with pervasive developmental disorders (PDDs) accompanied by mental retardation (MR, intelligence quotient [IQ]<70) (low-functioning PDD : LFPDD) or not accompanied by MR (IQ≧70) (high-functioning PDD : HFPDD). Prospective, non-randomized study of 24 children with LFPDD — 17 with autism and seven with PDDs not otherwise specified (PDDs-NOS) — and 14 children with HFPDD — 11 with PDDs-NOS and three with Asperger's disorders. Urinary 17-OHCS was measured between June 2002 and June 2004. In 21 of 24 LFPDD subjects and 8 of 14 HFPDD subjects a second measurement was taken 6 to 12-months after the first, after the subjects had received intervention for developmental disorders. Baseline urinary 17-OHCS levels in both LFPDD ($p<0.0005$) and HFPDD ($p<0.005$) were significantly higher than in controls. LFPDD subjects had significantly greater ($p<0.05$) levels of this stress hormone than did HFPDD subjects. Levels of 17-OHCS in both LFPDD ($p<0.05$) and HFPDD ($p<0.05$) decreased significantly after 6 to 12 months of intervention. PDD subjects showed higher levels of 17-OHCS than controls and showed a significant reduction in the level of stress indicator after they had received intervention for developmental disorders.

Key Words : pervasive developmental disorders, mental retardation, stress, 17-hydroxycorticosteroids, children

INTRODUCTION

Selye H[1] defined the three major clinicopathologcial signs of stress as atrophy of the lymph tissues, gastrointestinal bleeding, and aggravation of function in the adrenal cortex. Stress was considered to be the rate of wear and tear, and urinary 17-hydroxycorticosteroid (17-OHCS)[2] was considered an indicator of stress — i.e. a stress marker — although the diagnosis of stress had until then been based on the results of interviews or psychological tests. Urinary 17-OHCS/creatinine in patients with advanced cancer, severe diabetes mellitus, myocardial infarction, hypertension and obesity, alcohol abuse, or psychosocial stress[3] was higher than in age-matched controls. However, there is no report concerned with urinary 17-OHCS/creatinine in children with pervasive developmental disorder (PDD). Currently, the diagnosis of PDD is based on parent interviews, questionnaires, and direct observations in accordance with the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. To our

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knowledge, there is no biological index for the diagnosis of PDD.

Our objective was to compare the urinary levels of stress (17-OHCS) in PDD subjects with mental retardation (MR, intelligence quotient [IQ]<70) (low-functioning PDD : LFPDD), PDD subjects without MR (IQ≧70) (high-functioning PDD : HFPDD), and controls. PDDs include autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder and PDDs not otherwise specified (PDD-NOSs). No subjects with Rett's disorder or childhood disintegrative disorder were included in this study.

In this study we also evaluated and compared urinary levels of stress hormone in children with PDDs after receiving behavioral or environmental intervention.

MATERIALS AND METHODS

We measured urinary 17-OHCS[2] in children with PDDs between June 2002 and June 2004. Levels were measured in 24 children with LFPDD and 14 with HFPDD (Table 1). The mean age of LFPDD subjects was 5.4 years (SD=2.2), and their mean IQ was 51 (SD=14). The mean age of HFPDD subjects was 6.6 years (SD=2.0), and their mean IQ was 94 (SD=12). We used the Tanaka-Binet for less than six years of age or WISC-III test for more than six years of age as an IQ test.

Levels were measured a second time in 21 of the 24 LFPDD subjects and 8 of the 14 HFPDD subjects 6 to 12- months after the first, after the subjects had received intervention for developmental disorders ; for various reasons the remainder did not return to our outpatient clinic. The second urinalyses were performed 6 to 12-months after the first ones, after the subjects had received behavioral, environmental and/or drug intervention for their developmental disorders. This was not a 24 hour urinary cortisol assessment. We used samples of urine accumulated in the bladder overnight and collected in the morning. Each urine sample was collected from bedtime until rising in the morning, and 80 ml was used. Diagnosis of PDD was based on the results of interviews, questionnaires, and direct observation by DSM- Ⅳ criteria ; MR was diagnosed by IQ<70[4]. As controls, we measured the morning urine from 11 typically developed children with a mean age of 7.8years (SD=2.1). The control group was recruited from the renal clinic of our hospital. All control children were in a chronic state, and their urine examination did not reveal any abnormalities. The urine data were not influenced by collection season or day of the week. Urinary 17-OHCS levels in the controls were unchanged before and after staying out overnight. In typically developed children, the 17-OHCS/creatinine showed no difference by age[5].

All children lived at home and traveled to their places of intervention, and to their community preschools or primary schools. They had a regular consultation for developmental delay at a child guidance clinic or public health center once a month and a public health nurse visited home or community preschool or primary school for an interview. Some children went to special classes or schools for mentally or physically handicapped children.

Twenty of the 24 LFPDD subjects and 8 of the 14 HFPDD subjects had chief complaints of speech delay or communication disorder. The most notable behavioral peculiarities in our subjects were compulsions to line things up exactly or watch revolving objects such as fans in ventilators. Subjects tended to draw two-dimensional pictures, a picture of a catalog, a picture of poor body image, or an accurate picture.

In our hospital, the main therapy for PDD subjects in the first 6 months was modification of the living environment, including regulation of the circadian rhythm. Circadian rhythm was irregular in 12 of 24 LFPDD subjects and three of 14 HFPDD subjects at the time of the first medical examination. We defined irregular circadian rhythm as being awake past 10 p.m. or asleep past 8 a.m.. We recommended going to bed early and getting up early. We used a sleep-wakefulness cycle diary to check the bedtime and the time of rising in the morning. We also recommended that subjects not spend large periods of time watching TV ; we aimed for less than 2 hours a day. We also aimed to enhance the range of everyday activities. None of the subjects were receiving drugs at the time they enrolled in this study. Drug therapy was used mainly used for hyperkinesias with methylphenidate or for aggressive behavior with haloperidol. Habilitation by sensory integration training was not used at our hospital.

表 1 Characteristics of Patients and Controls

Subjects	Age at onset (years)	Sex	Diagnosis	IQ or DQ	Chief complaints	Urinary17-OHCS/creatinine [mg/g * cre]	
						Before intervention	After intervention
LFPDD							
1	4	M	Autism	50	Speech delay, hyperactivity	7.35	4.208
2	11	M	PDDNOS, MR, CD	52	Quick to take offense, violence	6.458	5.713
3	5	M	Autism	51	Speech delay, irregular circadian rhythm	13.856	7.766
4	5	M	Autism	63	Communication disorder	12	9.279
5	7	F	Autism	56	Speech delay	12.937	6.804
6	5	M	Autism	65	Playing alone in kindergarten	8.272	6.466
7	5	M	PDDNOS, MR	68	Speech delay, echolaria	4.612	4.826
8	4	M	PDDNOS, MR	53	Communication disorder	13.802	7.714
9	5	M	Autism	53	Speech delay	7.489	7.214
10	5	M	Autism	69	Speech delay	7.181	5.018
11	4	M	Autism	40	Speech delay	15.5	5.743
12	6	M	Autism	45	Speech delay	4.672	5.451
13	6	M	PDDNOS, MR	20	Speech delay, insensitiveness, minor anomaly	6.819	5.805
14	3	M	Autism	60	Speech delay	9.517	8.561
15	3	F	PDDNOS, MR	63	Nystagmus, persistence	10.427	12.342
16	11	F	Autism	45	Speech delay	4.881	5.912
17	5	M	Autism	45	Speech delay	8.411	11.363
18	3	M	PDDNOS, MR	66	Speech delay, poor eye contact	6.11	7.268
19	8	M	Autism	62	Speech delay	5.546	4.993
20	5	F	Autism	28	Floppy infant	13.109	8.066
21	6	M	Autism	29	Speech delay, speaking loudly	6.361	4.838
22	3	F	Autism	49	Speech delay, delayed sleep phase	5	ND
23	3	M	Autism	35	Speech delay	3.584	ND
24	7	M	PDDNOS, MR	65	Communication disorder	7.996	ND
HFPDD							
1	7	M	HFPDD	83	Communication disorder	3.868	4.027
2	8	M	Asperger syndrome	91	Hyperactivity	4.889	4.027
3	10	F	HFPDD	100	Attention deficit disorder	5.676	4.529
4	8	M	HFPDD	92	Speech delay	5.135	4.157
5	10	M	HFPDD	78	Communication disorder	5.745	5.506
6	5	F	HFPDD	94	Speech delay, hyperactivity	9.916	6.544
7	4	M	HFPDD	99	Speech delay	9.098	4.906
8	7	M	HFPDD, ODD	76	Speech delay, hyperactivity	6.641	4.702
9	4	F	HFPDD	120	Speech delay	9.214	ND
10	7	M	HFPDD	92	Speech delay	5.831	ND
11	4	F	HFPDD	79	Hyperactivity	3.688	ND
12	6	M	Asperger syndrome	102	Hyperactivity	6.801	ND
13	6	F	Asperger syndrome	103	Playing alone	4.688	ND
14	6	M	HFPDD	101	Pronounce a word unclearly	6.385	ND
Control							
1	8	M		ND		3.519	ND
2	8	M		ND		4.547	ND
3	8	F		ND		5.186	ND
4	10	M		ND		4.786	ND
5	3	M		ND		3.622	ND
6	10	M		ND		4.379	ND
7	9	F		ND		2.692	ND
8	10	F		ND		3.139	ND
9	6	F		ND		5.827	ND
10	6	M		ND		5.27	ND
11	8	M		ND		3.798	3.523

LFPDD, low functional pervasive developmental disorder ; HFPDD, high functional pervasive developmental disorder ; M, male ; F, female ; PDDNOS, pervasive developmental disorder not otherwise specified ; MR, mental retardation ; CD, conduct disorder ; ODD, oppositional defiant disorder ; ND, not done

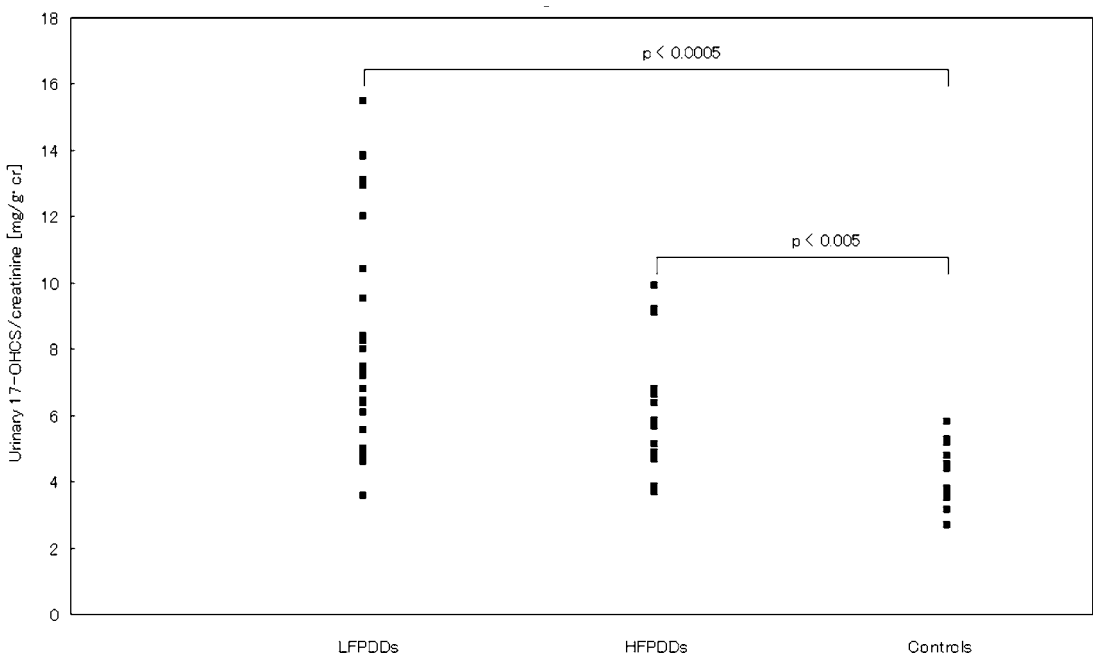

Fig. 1 Urinary 17-OHCS/creatinine in LFPDDs (n=24), HFPDDs (n=14) and controls (n=11)

Violent or hypersensitive behavior can make it hard to take blood samples or saliva samples from patients with PDD. Blood samples must be taken in the hospital, but urine samples can easily be obtained at home. Saliva samples were very difficult to take in large quantities. We therefore considered that urine samples were the best for checking PDD patients for stress. We chose morning urine because we considered that nocturnally accumulated urine samples would be the most stable. In addition, excretion volume of 17-OHCS increases in the morning and decreases in the night. So we chose morning urine which showed the highest level in a day. We examined urinary 17-OHCS and creatinine levels simultaneously and calculated the ratios of urinary 17-OHCS to urinary creatinine. The units [mg/g・creatinine] that we used were very stable, because the values were divided by those of urinary creatinine. By calculating the ratio of urinary 17-OHCS to urinary creatinine, we lessened the influence of sex or physique. Urinary 17-OHCS was measured by an improved method based on the Porter-Silber reaction[2] in which the inter-assay variance was 3.71%. Urinary creatinine was measured with an autoanalyzer (JEOL BM 1650, Tokyo, Japan). Urinary 17-OHCS and creatinine were measured by Sumikin Bio-Science, Incorporated (Sagamihara, Japan).

Values in the two treatment groups (LFPDD and HFPDD) and controls were compared by the Mann-Whitney non-parametric test, and the values between two data collection points in the two treatment groups (LFPDD and HFPDD) were compared by the Wilcoxon non-parametric test. Statistical significance was established at the $p<0.05$ level. We did not hold an ethical committee meeting in this study, but we orally took an informed consent from all patients' parents, and they agreed to our study.

RESULTS

As a stress indicator, urinary 17-OHCS concentration in LFPDD at baseline was significantly ($p<0.0005$) higher than in controls (Fig. 1). Urinary 17-OHCS concentration in HFPDD at baseline was significantly ($p<0.005$) greater than in controls (Fig 1). Moreover, urinary 17-OHCS concentration in LFPDD was significantly greater than in HFPDD ($p<0.05$) (Fig. 1).

After subjects had received intervention for 6 to 12 months, both LFPDD and HFPDD subjects had significantly ($p<0.05$) lower levels of 17-OHCS than before intervention (Fig. 2, 3). In LFPDD there was no significant difference in 17-OHCS level between medicated subjects (n=8) and unmedicated subjects (n=13).

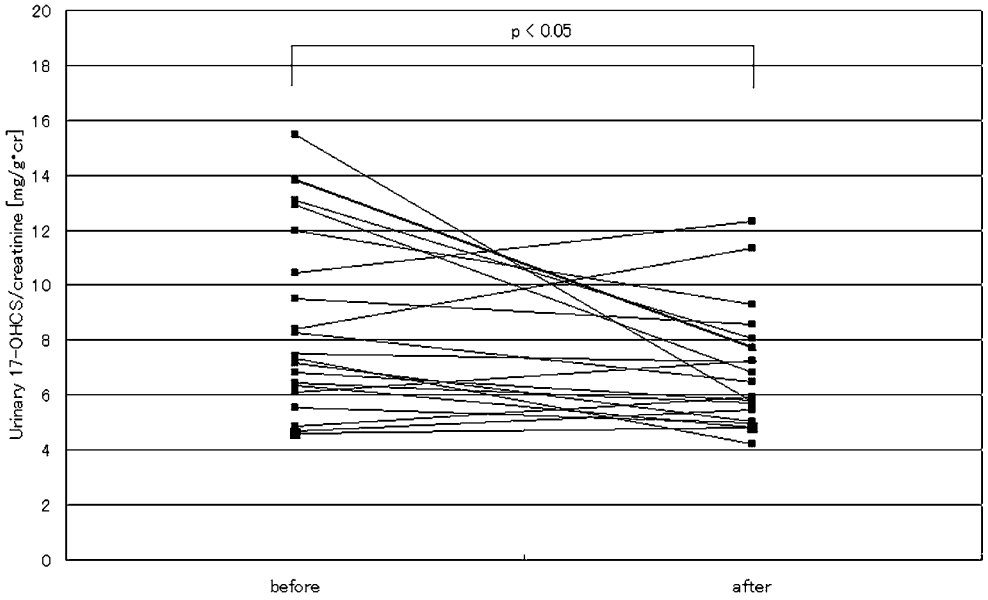

Fig. 2 Changes of urinary 17-OHCS/creatinine in LFPDDs (n=21)

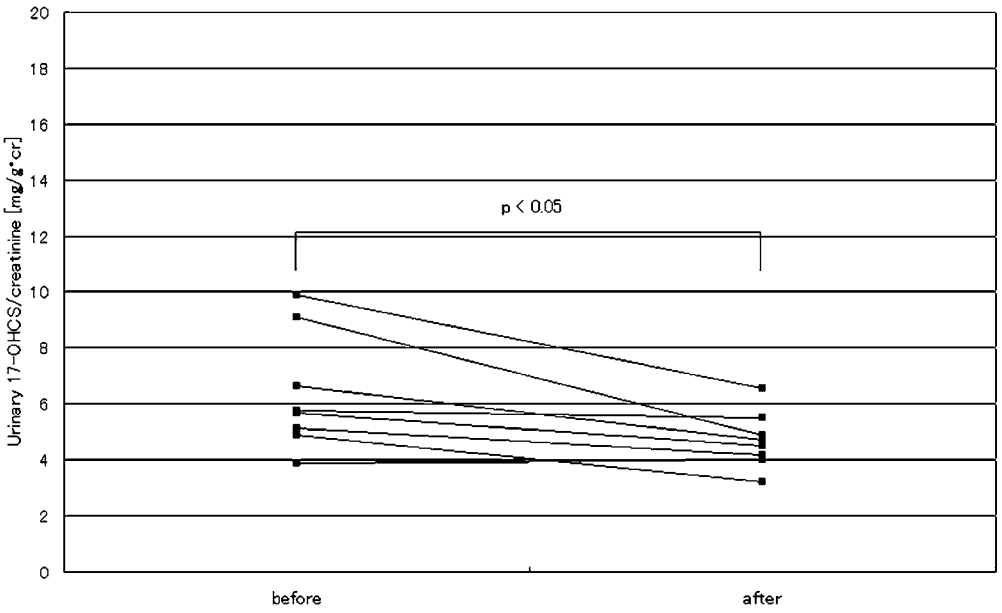

Fig. 3 Changes of urinary 17-OHCS/creatinine in HFPDDs (n=8)

DISCUSSION

Selye H[1] regarded stress as the rate of wear and tear and 17-OHCS as its indicator, and urinary 17-OHCS/creatinine was higher than in age-related controls in patients with advanced cancer, severe diabetes mellitus, myocardial infarction, hypertension and obesity, alcohol abuse, or psychosocial stress[3]. Stress indicators have been studied in adult subjects or parents of children with PDD before[6~9]. However, there is only one report[5] in which specimens of morning urine were used to examine stress in children with atopic dermatitis or renal disease. Our objective was to compare the degree of stress in PDD subjects and controls by examining urinary 17-OHCS level. There have been no reports of urine stress marker examination in children with PDDs, and we believe that our study is the first report of the importance of examining urinary stress markers in children with PDD.

After diagnosis, virtually all of our subjects with LF-

PDD and some with HFPDDs had received special assistance at community preschools or primary schools with extra staff. Since we explain the details of PDD to the patient's parents and school teachers, it can establish a good parent-child and teacher-student relationship. We consider that these are the main factors of decreasing stress indicator levels in patients with PDD. Health examinations of infants in Japan are done at less than 1 year of age, and again at 1 year and 6 months and then at 3 years. There is no subsequent health examination before the child enters school at age 6 years. Infants who fail to pass the health examination at age 3 years almost always fail because of speech delay, and some of these infants have LFPDD, but not HFPDD in our country. LFPDD children tend to receive intervention for developmental disorders earlier than do HFPDD ones. However, our LFPDD subjects showed greater stress than HFPDD subjects. Almost all HFPDD children are diagnosed after they enter school, so since 2006 we have been performing a health examination at age 5 years to pick up these HFPDD children early.

Medication does not cure PDD, but some drugs can be useful in the management of behavioral problems[10]. We use methylphenidate for hyperactivity therapy, but only in LFPDD patients. We considered that therapy with methylphenidate did not influence urinary 17-OHCS levels, because there was no significant difference in levels between the medicated and unmedicated groups. Therefore, we considered that stress in PDD subjects decreased significantly only because of the behavioral or environmental intervention, not because of the drug treatment.

We used urine samples in this study, because most PDD children show violent and hypersensitive behavior, which can make it very hard to take plasma samples or saliva samples. Urinary 17-OHCS and blood cortisol were a compound related to "wear and tear" to stress, and in typically developed children, the 17-OHCS/creatinine showed no difference by age[5]. We could not take second urine samples from the comparison group, except one sample because of being transferred to another hospital. Urinary 17-OHCS of one control is measured at December 2, 2002, December 7, 2002 and November 20, 2003. And urinary 17-OHCS/creatinine level showed 3.578, 3.798 and 3.523, respectively. There is no change of urinary 17-OHCS level in one control after one year. It is necessary to accumulate more control data in the future.

None of our patients had midline anomalies in the brain and the body. We therefore considered that they had no monoamine secretion abnormalities due to abnormalities of the posterior nuclei of the brainstem. Levels of serotonin, a monoamine present in the midline of the brainstem, are influenced by changes in the living environment[11,12]. Therefore, serotonin in our patients is not influenced by midline anomaly. We therefore advised our patients and their parents to regulate the patients' living environments or rhythms for at least 6 months, for example by limiting the time spent watching TV to no more than 2 h and regulating the circadian rhythms to activate serotonine. In typically developed children, urinary 17-OHCS level as a stress barometer shows no age-related changes[5]. Stress indicator levels in our patients decreased over the 6 months or more of intervention through the application of these measures. It is not known whether activation of serotonin lessens the urinary concentration of stress hormones.

Although we defined MR as IQ$<$70, some patients with LFPDD who had IQs on the 60 mark increased their IQs to over 70 after receiving intervention for developmental disorders. For the purposes of this study we still defined these patients as having LFPDD.

We concluded that PDD subjects had significantly lower urinary levels of stress hormone after receiving behavioral or environmental intervention. Most of these PDD children—mainly those with LFPDD—and their parents are stressed to some degree, and some parents or teachers treat them with psychological cruelty. These events lead to a vicious circle. Therefore, it can be argued that LFPDD children need even more urgent intervention for their developmental disorders than do HFPDD children.

Early detection and attention are necessary, but few pediatricians in Japan can diagnose PDD, because it is a difficult condition to diagnose and requires diagnostic experience. It is very important for parents or teachers to notice signs of PDD in infancy. Parents need to obtain an early consultation with a medical specialist in PDD through their local physician. Hopefully this will decrease the stress in PDD children and allow

them to adapt more readily to school life.

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