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## Endocrinological Analyses of Mental Disorders in Adolescence: Changes of Steroid Metabolite (Urinary 17KS) Levels in the Urine

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**Abstract** Adolescence is expected to have different endocrinological patterns from adults. In this study, we monitored the urinary 17KS fractions of healthy adolescent volunteers (12-18 years old) and patients with psychological disorders (13-18 years old). The ratio of androsterone to etiocholanolone (A/E) in the male adolescent volunteers was nearly the same as that in adult males, and A/E in the female adolescent volunteers was lower than adult females. The ratios in adolescent patients did not differ significantly from the levels in the normal volunteers, but there was a clear tendency between patients' symptoms and level of A/E : patients with higher A/E had aggressive symptoms (e.g., violence to family), and patients with lower A/E had such symptoms as anxiety, depression, common neurosis, and dissociative disorders.

In order to evaluate the patient's true condition, a physically evaluable index which represents different mental state should be established. Urinary fractions of 17KS and A/E could be useful in understanding the mental conditions of patients and in prescribing appropriate therapy.

*Key Words* : Periodical psychosis, Adolescence, Urinary 17KS, Androsterone, Etiocholanolone

### Introduction

Periodical psychosis in adolescence clinically presents the manic-depressive state or oneirismic state, and these psychological conditions are repeated periodically<sup>(1-3)</sup>. The oneirismic state is associated with hallucinations/delusions or consciousness disorders.

These patients usually have functional abnormalities in the hypothalamus-pituitary system, which are indicated by (i) long-term continuation of abnormal fractions of serum estrogen, (ii) abnormal findings in blood and biochemical tests, which are thought to be related to the degree of mental disorder and

speed of its development, (iii) abnormal fraction of urinary 17-ketosteroid (17KS), and (iv) abnormal findings in stress loading tests, etc.<sup>(4-7)</sup>. Therefore, the relationship between psychological symptoms and endocrinological findings in these patients should be investigated<sup>(8-13)</sup>.

In the case of the urinary 17KS fraction, the ratio of androsterone to etiocholanolone is called the androgen index, A/E, and it is thought to change along with the state of the adjustment function of the hypothalamus-pituitary-adrenal system as well as the metabolic state in the liver. It has also been reported that A/E in the stage of sudden deteriora-

tion of periodical psychosis decreased below 1.5, and it fluctuated with the changes in symptoms<sup>(9-10)</sup>. In our past experiences, there have been several patients whose A/E levels increased when psychiatric symptoms were relieved. In the discussin section, some cases are briefly introduced. Therefore, we judged that abnormal urinary 17KS fractions are related to psychological symptoms, and its monitoring could be useful in identifying the state of disorders and condition of physical adjustment functions. In past studies, normal A/E level have only been reported for adults, i.e.,  $\geq 1.5$ , and not for adolescent of pubertal children.

In this study, we investigated the 17KS fraction in normal students (12-18 years old), as well as age-matched patients who received psychotherapy either as outpatients or as inpatients. We theorized that abnormal A/E levels could be observed in some treated cases even when hormonal abnormality, as observed adolescent periodical psychosis, was not present.

## Subjects

The normal group consisted of healthy volunteers, 16 males and 14 females between 12-18 years old (average 15.0 for male, and 15.1 for female). Volunteers were introduced through hospital employees. Almost all male students who received participation requests for this study complied. On the other hand, approximately half of the female students refused. Mental and physical conditions before the study was started were asked by questionnaire to all volunteers, and no complaints were made concerning thier conditions.

The patient group consisted of 15 males and 17 female, 13-18 years old, who visited our hospital during May 1989 to August 1989. Those patients who received anti-depressants, anti-psychotics, or anti-epileptics were excluded from the study subjects.

## Method

We recorded the time of 1st urine of Day 1 at the rising in the morning. The urine of each

subject was collected through 24 hours from the 2nd urine of Day 1 to the urine of Day 2 at the exact same time of the 1st urine of Day 1, stored in a refrigerator, and the total was regarded as daily urine. After freezing, the daily urine was processing the oxygen decomposition method, and then its 7 fractions of 17KS were monitored by gas chromatography. The total of each fraction was regarded as the volume of 17KS.<sup>(14)</sup>

## Results

### (1) 17KS Fractions

Normal Group : The volume of 17KS of normal male students on the average was  $3.46 \pm 2.07$  mg/day, which was near the lowest normal levels in adult male volunteers (Table 1)<sup>(15,16)</sup>. The 17KS level increased according to age ( $\gamma=0.84$ ), and the levels in young normal volunteers were even lower than the normal lowest level in adults(Fig. 1). The volume of 17KS also correlated to height and body weight. The volume of 17KS in each fraction of the normal group was also near the lowest levels of normal adults.

In normal female students, the total as well as the volume of each fraction was located in the middle to low level of the normal range for adult females. The average total volum of 17KS was  $3.39 \pm 1.79$ mg/day (Table 2). This volume increased according to age ( $\gamma=0.5$ ), and younger students often had lower volumes than the lowest normal level of adult females (Fig. 1).

The A/E of normal male students was  $2.3 \pm 0.9$  (mean  $\pm$  S.D.), and 15 of the 16 students had levels higher than 1.5. In normal

Table. 1 The volume of 17KS of normal male adults and normal male students

	normal level	normal	
	in adults	students	%
	mg/day	mg/day	AVG STD
total 17KS	2.0-7.6	3.46 $\pm$ 2.07	
androsterone	1.10-4.20	1.61 $\pm$ 0.95	46 $\pm$ 10
etiocholanolone	0.55-2.60	0.74 $\pm$ 0.47	21 $\pm$ 4
dehydroepiandrosterone	0.12-5.20	0.12 $\pm$ 0.11	3 $\pm$ 3
11-ketoandrosterone	$\leq$ 0.12	0.03 $\pm$ 0.02	1 $\pm$ 0
11-ketoetiocholanolone	0.04-0.65	0.17 $\pm$ 0.21	4 $\pm$ 3
11-hydroxyandrosterone	0.40-2.30	0.73 $\pm$ 0.42	23 $\pm$ 7
11-hydroxyetiocholanolone	0.03-0.65	0.11 $\pm$ 0.16	2 $\pm$ 2

female students, the A/E on average was  $1.6 \pm 0.8$  (mean  $\pm$  S.D.), and 8 of the 14 students had levels below 1.5 (Fig. 2 and 3). The correlation between A/E and age was not significant, i.e.,  $\gamma = -0.03$  for males, and  $\gamma = -0.22$  for females (Fig. 4). There was also

no correlation coefficient between the daily volume of urinary 17KS and A/E.

Table. 2 The volume of 17KS of normal female adults and normal male students

	normal level		% AVG STD
	in adults mg/day	normal students mg/day	
total 17KS	0.5-6.5	3.39 $\pm$ 1.79	
androsterone	0.40-3.00	1.21 $\pm$ 0.76	36 $\pm$ 8
etiocholanolone	0.30-2.50	0.94 $\pm$ 0.64	26 $\pm$ 7
dehydroepiandrosterone	0.04-2.60	0.16 $\pm$ 0.23	4 $\pm$ 5
11-ketoandrosterone	$\leq 0.07$	0.02 $\pm$ 0.01	1 $\pm$ 0
11-ketoetiocholanolone	0.30-0.50	0.22 $\pm$ 0.22	6 $\pm$ 4
11-hydroxyandrosterone	0.22-1.60	0.70 $\pm$ 0.28	23 $\pm$ 6
11-hydroxyetiocholanolone	0.02-0.65	0.15 $\pm$ 0.19	4 $\pm$ 4

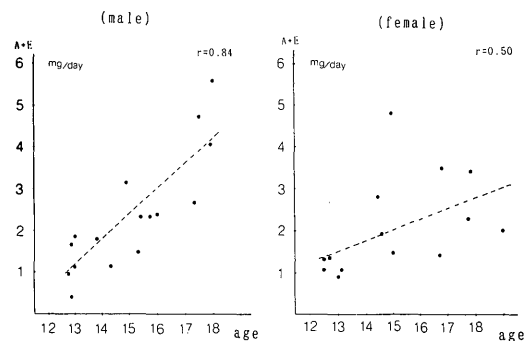


Fig. 1 Urinary total 17-ketosteroid secretion and age in normal subjects (Androsterone + Etiocholanolone)

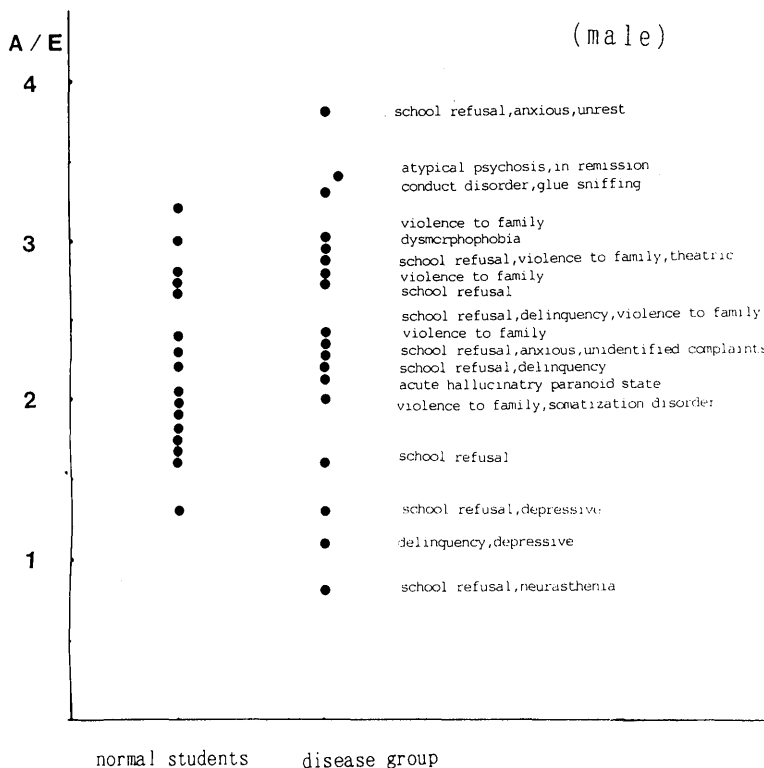


Fig. 2 Urinary androgen index

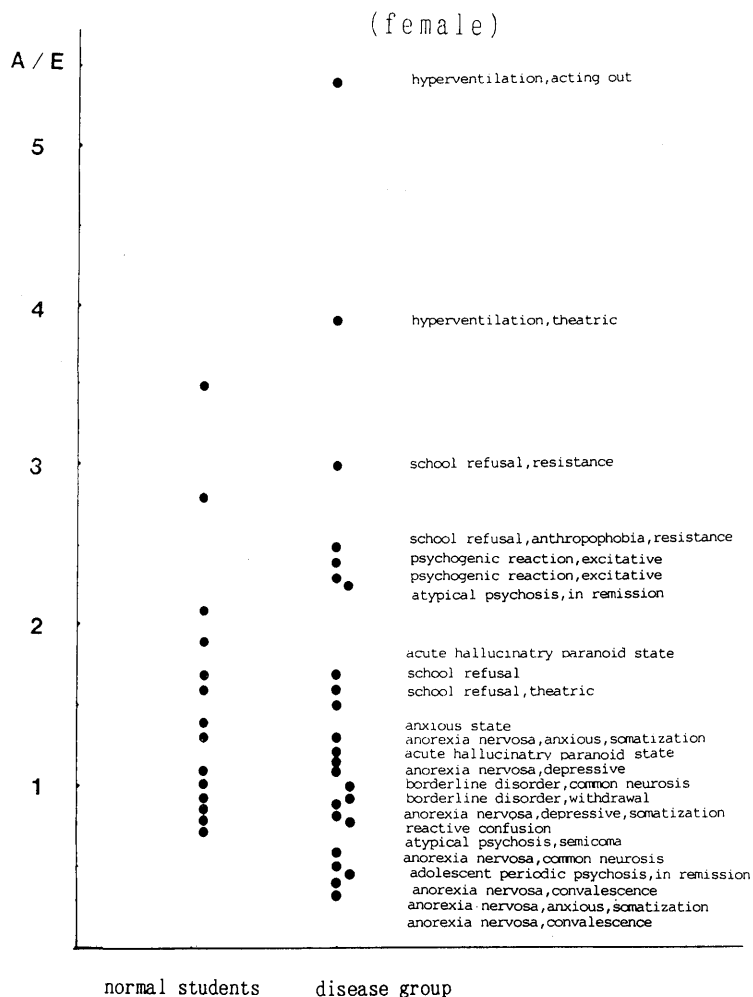


Fig. 3 Urinary androgen index (female)

Disease Group : For male subjects (average age: 14.5 years), there were no specific findings on the average  $\pm$ S.D. of the 17KS volume in each fraction. Their figures were nearly the same as those in the normal group (Table 3). In female subjects (average age: 17.1 years), the volumes in each fraction was higher than those of the normal group. However, they did not show any significant differences after the adjustment of data to age. The rate of each fraction to the total 17KS also showed no significant difference from the normal group, even though the S.D. was

slightly larger in the disease group (Table 4).

Comparisons between females and males in the disease group, and between A/E and age, did not show any differences or correlations. (2) *A/E level*

A/E levels in the normal and disease groups were compared in Fig. 2 and 3. The psychiatric situation of each patient is listed next to each mark. In male patients, the A/E tended to be high when they showed "violence to family", "delinquency", or other misdemeanor actions, and to be low when they showed "depressive symptoms". In female

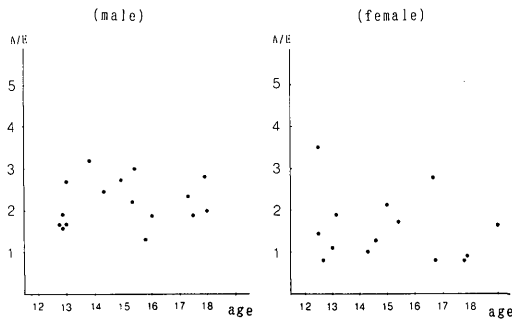


Fig. 4 Urinary androgen index and age

Table. 3 The volume of 17KS of normal male students and male disease group

	normal students		disease group	
	mg/day	%	mg/day	%
total 17KS	3.46±2.07		3.79±1.68	
androsterone	1.61±0.95	46±10	1.64±0.88	42±11
etiocholanolone	0.74±0.47	21±4	0.73±0.39	19±6
dehydroepiandrosterone	0.12±0.11	3±3	0.27±0.23	5±4
11-ketoandrosterone	0.03±0.02	1±0	0.05±0.03	1±1
11-ketoetiocholanolone	0.17±0.21	4±3	0.22±0.15	7±6
11-hydroxyandrosterone	0.73±0.42	23±7	0.88±0.40	23±9
11-hydroxyetiocholanolone	0.11±0.16	2±2	0.11±0.14	3±4

Table. 4 The volume of 17KS of normal female students and female disease group

	normal students		disease group	
	mg/day	%	mg/day	%
total 17KS	3.39±1.79		4.11±2.58	
androsterone	1.21±0.76	36±8	1.60±1.25	36±13
etiocholanolone	0.94±0.62	26±7	1.22±0.83	31±13
dehydroepiandrosterone	0.16±0.23	4±5	0.24±0.45	4±4
11-ketoandrosterone	0.02±0.01	1±0	0.04±0.04	1±1
11-ketoetiocholanolone	0.22±0.22	6±4	0.19±0.12	5±3
11-hydroxyandrosterone	0.70±0.28	23±6	0.78±0.52	20±11
11-hydroxyetiocholanolone	0.15±0.19	4±4	0.11±0.10	3±4

patients, the A/E tended to be high in those who had hyperventilation syndrom, hyperactivity, contrived reactions, resistance to parents/teachers, repeated escape from the hospital, etc. On the country, the A/E was low in those patients who were in the state of anxiety, depression, common neurosis, or who had dissociative disorders. Patients with feeding disturbances had low A/E. Most investigated patients were obedient and none were violent or had bulimia. In Fig. 4, "convalescence" meant patients who started to have meals in a ward with other patients.

In these ways, different symptoms seemed to appear according to the A/E level. Both male and female patients had very small volumes of steroid metabolites except androsterone, etiocholanolone, and 11-hydroxyandrosterone. There were no clear relationships between symptoms and each fraction of 11-hydroxyandrosterone.

### Discussion

#### (1) Urinary 17KS as an indicator of psychological status

In past studies, A/E was reported as more than 1.5 in normal adult and less than 1.5 in patients at the stage of sudden deterioration of periodical psychiatric symptoms<sup>(9,10)</sup>. The biological meaning of the A/E index has not been clarified but it is thought to express certain physical changes along with psychological symptoms. In the past observation on periodical psychosis in adolescence who received no medication, we monitored changes in symptoms, serum estrogen fractions, and A/E.

In one patient, A/E sometimes fell lower than 1.5 during the course of observation, but increased as the patient achieved overall improvement of a good social adaptation. On the other hand, another patient whose A/E continued to be low and did not increase during the course of observation, did not achieve social adaptation. Therefore, we believe that there is some relationship between the A/E level and the prognosis of periodical psychosis in adolescence.

We also observed A/E in 2 borderline adolescent cases whose A/E were low at the early stage of treatment, and then increased when their psychological states were improved after long-term psychotherapy. In the first case, the A/E was 0.7 and 0.9 when the patient experienced common neurosis and hallucination, then it increased to 1.3 after 2 years of treatment. In the second case, the A/E was 1.0 at the withdrawal period, and then increased to 1.6 after 6 months of treatment. In addition, another patients with atypical psychosis had a episode of mutism and akinesia for 6 months. Her serum estrogen fraction and findings of hypothalamus-pituitary function tests were

all normal. After carbamazepine administration, she was relieved of mutism and akinesia and achieved good school and social adaptation. Her A/E was 0.8 at the disease period, but increased to 2.3 at 4 months after returning to normal daily life. These cases also indicate the relationship between A/E in the urinary 17KS fraction and psychological symptoms.

### (2) Measurement of urinary 17KS

Measurement of serum steroid, especially when the stress test is performed, can accurately show the level of steroid and the overall physical state including the hypothalamus-pituitary-adrenal system at the time of monitoring. However, since steroid is secreted intermittently, its serum level fluctuates greatly even in the course of one day. Consequently, it is not easy to clarify the relationship between the monitored level at a certain time and the overall physical and psychological state of the patient. In addition, frequent blood sampling causes patients additional stress. On the other hand, the measurement of urinary steroid level using stored urine (in this study, for 24 hours) can detect the daily level on an average basis.

The causes of the abnormalities of urinary 17KS are explained by or are presumed to be due to abnormalities in the hypothalamus-pituitary system, the adrenal cortex, the gonadal system, or in the metabolism of steroid hormones in the liver<sup>(13-16)</sup>. However, abnormalities in fractions have not yet been explained in detail.

The hypothalamus-pituitary system is closely related to the daily rhythm of the body, and its involvement in periodical psychosis in adolescence has been indicated as symptoms show certain changes within one day's time. Blood and biochemical findings also show that abnormalities in test results are more significant when the degree and rate of psychic deterioration increases. In addition, it is known that (i) these patients show subclinical hypothyroidism, (ii) they have abnormal fractions of urinary 17KS which indicate deterioration of hepatocerebral homeostasis, (iii) there are long-term abnormalities in the serum estrogen fraction, and (iv) there could be a relationship between

time and psychiatric symptoms. Therefore, investigations into the normal levels of healthy volunteers as well as clear understandings of those levels in patients are thought to be important<sup>(11)</sup>.

### (3) Healthy students

Only a few male students refused to be volunteers: the major reason was the "impossibility of storing urine during school events". On the other hand, nearly half of the female students refused the request: their reasons were "hygiene", "inconvenience", and "no desire to participate".

The urinary 17KS volume increased with age in both male and female volunteers, which indicated the growth process of adrenal and gonad systems in adolescence<sup>(14-16)</sup>. This volume also showed a correlation with heights and body weights.

A/E was  $\geq 1.5$  in male students, and this level was the same as adult males. On the other hand, the A/E in female students was lower than adult females. Therefore, though the level was lower than 1.5, it did not necessarily indicate abnormalities in female students. Contrasting with the urinary 17KS volume, the A/E was not related to age, height, or body weights in both males and females.

### (4) Patients

The urinary 17KS volumes of patients were within the normal range except of those of early teenagers and those who had small urine volumes. Patients tended to have different symptoms were delinquency, excitation, hyperactivity, or resistance tended to have high A/E levels, whereas those with depression or neurosis had low A/E levels. In addition, some patients who showed improvement with short-term treatment in our outpatient office did not have low A/E levels.

These differences in A/E indicate the possible relationships between psychiatric imbalance and physical imbalance in hypothalamus-pituitary-adrenal-gonad-liver functions.

The subject patients in this study did not have endocrinological disorders, and their urinary 17KS volumes were within the normal range. In the future, the symptoms and

changes of the 17KS volume and A/E should be observed in detail. In addition, the mechanisms of the interrelationship between psychiatric symptoms and 17KS or A/E should be clarified through stimulation tests on the liver and on the hypothalamus-pituitary-adrenal-gonad system, or through animal experiments.

We investigated the mental conditions of each age group of healthy students through psychological tests. In this field, it is necessary to establish a physical index which relates to the mental state. As a method to get such an index, the monitoring of urine substances could be useful as it has much less effect on the subjects as compared to the measurement of serum substances. If physicians were to have such a physical index showing mental states, the patient's conditions could be evaluated based on not only the verbal explanations made by patients or their families, but through objective data. This would be a great help in understanding the true condition of patients and in prescribing appropriate therapy.

### Summary

In this study, the urinary 17KS fraction was investigated in order to observe the adolescent endocrinological conditions of mental disorders. The androgen index A/E in the urinary 17KS fraction was investigated in order to observe the adolescent endocrinological conditions of mental disorders. The androgen index A/E in the urinary 17KS fraction is reported to decrease during the course of periodical psychosis in adolescence. Our findings and conclusion are summarized below.

- (1) In normal control subjects, the A/E in male students was  $2.3 \pm 0.9$  (mean  $\pm$  S.D.), and the A/E in female students was  $1.6 \pm 0.8$ .
- (2) The A/E for male patients showed no differences from the level of normal male subjects. In female patients, the mean level did not show any significant differences from that of normal females. However, the S.D. was larger.
- (3) Patients with high A/E had such symptoms as delinquency, violence, hyperactivity, resistance and the contrived reactions, whereas patients with low A/E had common neurosis and depressive tendencies.
- (4) By considering the relationship of adolescent

physical imbalance with mental disorders, physicians in therapy will be able to influence patient's reactions to family, school and society. Treatment policies and psychotherapy considering such physical imbalances will become more useful and effective than conventional treatment based on only the observation and/or evaluation of mental conditions.

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