

Original Article

Laboratory changes during ACTH therapy associated with renal calcified lesions

Running title: Laboratory changes during ACTH therapy

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Number of text pages, words, reference pages, tables, figures and legends to figures: 22 text pages, 2597 words, 2 reference pages, 3 tables, 2 figures and 2 legends to figures

Abstract

Background

Renal calcified lesions are known as one of the complications during adrenocorticotrophic hormone (ACTH) therapy for intractable epilepsy. However, laboratory changes during the therapy or laboratory features of high-risk cases with renal calcified lesions are yet to be clarified.

Methods

In this study, 43 patients with West syndrome ≤ 2 years were included. We retrospectively reviewed age and body mass index at the beginning of ACTH therapy, as well as the amount of fluid intake, daily urinary volume, and laboratory data during therapy. In addition, we studied the urinary sediment of the cases with renal calcified lesions diagnosed by computed tomography.

Results

After initiating ACTH treatment, urinary calcium (Ca)/creatinine ratio and urinary pH increased within 2 weeks. Urinary crystals and renal tubular epithelial cells (RTECs) in urinary sediment were frequently found in most cases. Urinary Ca levels, proteinuria or frequency of urinary crystals, and number of RTECs in the urinary sediment were significantly higher in patients with epithelial casts (ECs) or hematuria than in patients without these findings. Among the 7 patients who underwent abdominal CT, ECs or hematuria were found only those with renal calcified lesions. These findings suggested that patients with ECs or hematuria were more likely to have calcified lesions.

Conclusions

The risk of renal calcified lesions increases after 2 weeks of ACTH treatment. Abnormal findings in urinary sediments might be an early sign of renal calcification during ACTH therapy.

Key words: adrenocorticotrophic hormone therapy, calcium, crystals, renal tubular epithelial cells, urinary sediment

Introduction

Renal calcified lesions composed of calcium (Ca) and phosphate (P) can occur especially when zonisamide (ZNS) or topiramate (TPM) are combined with adrenocorticotrophic hormone (ACTH) therapy for the treatment of intractable epilepsy [1, 2]. However, there have been few reports on the changes in laboratory parameters relating to renal calcified lesions or laboratory features of patients with renal calcified lesions when treated with ACTH therapy alone [3].

An ultrasonography is often used when diagnosing renal calcified lesions; however, its sensitivity is insufficient [4]. Furthermore, infants with renal calcified lesions are often asymptomatic. To improve detection of patients with renal calcified lesions, simple and easy-to-use examinations are required.

Most renal calcified lesions are formed from deposition of crystals in the renal tubules [5]. During this process, changes in urinary sediment can be found [6, 7]. Although urinary sediment can be useful according to these facts, no studies have examined about urinary sediment during ACTH therapy in patients with renal calcified lesions.

Therefore, this study aimed to evaluate changes in laboratory values that are related to the development of renal calcified lesions during ACTH therapy without ZNS

or TPM. We also discussed the urinary features of high-risk patients with renal calcified lesions.

Methods

We retrospectively reviewed pediatric patients aged ≤ 2 years treated with ACTH therapy for West syndrome in Okayama University Hospital from January 2010 to December 2017. Patients who had premature discontinuation of ACTH therapy, those with calcified lesions or nephritis before ACTH therapy, and those with congenital diseases that can cause renal calcified lesions such as cystinuria, were excluded. Finally, 43 patients were included in this study. Synthetic ACTH administration was conducted intramuscularly once a day at a dose of 0.005 or 0.025 mg/kg/day. Dose of ACTH administration was decided depending on the severity and reactivity to treatment. Daily ACTH therapy was completed when the effect of the therapy for each patient reached a plateau. In the following week of treatment, we administered ACTH on alternating days. In our hospital, we administer ACTH daily for 4 weeks and on alternating days for 1 week for most of the cases. During therapy, we obtained blood and urinary samples twice a week for most of the patients. We randomly examined the urine during daytime and used a urine bag to obtain urine because all patients were aged ≤ 2 years in this

study. Brain magnetic resonance imaging (MRI) or computed tomography (CT) were performed for all patients to evaluate brain shrinkage after the treatment.

Sex, age, and standard deviation (SD) score of body mass index (BMI) calculated by using “Excel-based Clinical Tools for Growth Evaluation of Children” made by The Japanese Society for Pediatric Endocrinology (taikakushisu_v3.3.xlsx, version 3.3 http://jspe.umin.jp/medical/chart_dl.html), were recorded at the beginning of ACTH therapy. We also collected data on the amount of fluid intake, daily urinary volume, and laboratory data before and during therapy. Laboratory data included calcium and phosphate levels in serum and urine, urinary Ca/creatinine (Ca/Cr) ratio, urinary P/creatinine (P/Cr) ratio, urinary pH, renal tubular reabsorption rate of Ca and P (%TRCa and %TRP, respectively), and urinary sediment and quantitative test of urine. We examined laboratory data that were measured within one month before ACTH therapy and during the therapy. We examined sequential findings on the urinary sediment during therapy in 7 patients who underwent abdominal CT examination. We also examined the side effects of ACTH therapy, including irritation, hypokalemia, hypertension, brain shrinkage, and epithelial casts (ECs) or hematuria in urinary sediment, in addition to renal calcified lesions.

Although nephrocalcinosis (NC), nephrolithiasis (NL), and urolithiasis (UL) develop due to a common cause and often coexist, we defined NL and UL as a solid stone appearing in the kidneys and urinary tracts, respectively, and we defined NC as small deposits of calcification in the renal parenchyma. We defined calcified lesions as including NL, UL, and NC. Abdominal CT was performed for 7 patients within 50 days after ACTH therapy. The decision to perform abdominal CT is depending on each physician's discretion.

Regarding the urinary sediment, we adopted the guideline of the Japanese Committee for Clinical Laboratory Standards (<https://doi.org/10.14932/jamt.17J1-1e>). Hematuria and renal tubular epithelial cells (RTECs) were defined as ≥ 5 red blood cells and ≥ 1 RTECs per high-power field (HPF) (400 \times magnification), respectively. In this study, we discriminate ECs from RTECs; we defined ECs as casts composed by RTECs and RTECs as scattered epithelial cells from renal tubules.

Hypertension was diagnosed when systolic or diastolic blood pressure increased above 95th percentile for age; we diagnosed as hypertention when systolic blood pressure reached ≥ 105 mmHg, or diastolic blood pressure reached ≥ 70 mmHg [8], or antihypertensive drug treatment.

Regarding the efficacy of the ACTH therapy, we judged the treatment as effective when epileptic seizures disappeared. We also examined the duration from the start of treatment to the onset of effects.

Statistical analysis

Numerical variables were compared using the Mann–Whitney U-test, whereas the categorical variables were compared using Fisher’s exact test in this study.

Laboratory data are reported as mean \pm standard error. Multivariate analysis was not performed because of the small sample size. We defined $P < 0.05$ as statistically significant. We used R commander (version 2.3–0) based on R (version 3.3.2, <http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html>). This study was approved by the Medicine Ethics Committee of Okayama University Hospital. All patients and/or their parents were informed about the study and given the option to refuse participation in this study.

Results

Laboratory data during ACTH therapy (Figure 1)

In our study, average duration of ACTH therapy was 34 days. Fluid intake and urinary volume increased after initiating therapy (Figure 1a, b). Serum Ca levels did not change during therapy (Figure 1c). After initiating ACTH therapy, urinary Ca level and Ca/Cr ratio were transiently decreased. After 2 weeks of treatment, although the urinary Ca level remained at the similar levels (Figure 1d), the Ca/Cr ratio in urine increased (Figure 1e), compared to the values before therapy. %TRCa gradually decreased within 2 weeks of treatment (Figure 1f). P levels in serum and urine decreased shortly after initiating treatment (Figure 1g, h). During treatment, %TRP decreased and urinary P/Cr ratio increased (Figure 1i, j). Urinary pH gradually increased after initiating ACTH therapy. The mean urinary pH increased to approximately 7.5 at one week after starting therapy and was maintained thereafter (Figure 1k).

As shown in Table 1, before ACTH therapy, there were no findings in the urinary sediment in most of the patients. In contrast, changes in urinary sediment were found in 40 (93%) patients during the therapy. ECs or hematuria was found in 13 patients and urinary crystals or RTECs preceded these findings.

Among the 7 patients who underwent abdominal CT, 4 had renal calcified lesions after therapy. All of the 4 patients had NC or NL and 2 had UL. Figure 2 shows the sequential findings in the urinary sediment in these 7 patients. Renal calcified

lesions were found in cases 1 to 4, but none were found in cases 5 to 7. In cases 1 to 4, ECs or hematuria preceded by crystals or RTECs were found. In the other 3 cases without renal calcified lesions, only the crystals or RTECs were found (Figure 2).

Clinical features of patients with ECs or hematuria (Table 2)

Given that ECs or hematuria were considered important after comparing the findings of 7 patients who underwent abdominal CT examination, all 43 patients were divided into the following 2 groups according to their urinary findings: patients with ECs or hematuria (group 1) during ACTH therapy and those without such finding (group 2). Groups 1 and 2 comprised 13 and 30 patients, respectively. In group 1, ECs and hematuria were found in 12 and 2 cases, respectively. The median of mean ECs of each case was 9 (1-27)/whole field. The mean red blood cell count of the 2 cases was 15 and 46/HPF, respectively. There were no differences in age and SD score of BMI when the treatment was initiated, and in the frequency of laboratory examinations between the groups. We found that urinary Ca levels, proteinuria, frequency of urinary crystals, and number of RTECs in the urinary sediment were significantly different between the 2 groups, as group 1 showed higher urinary Ca levels, tended to show proteinuria, and had

higher frequency of urinary crystals RTECs >4 /HPF. The urinary Ca/Cr ratio was not significantly different between the 2 groups.

Duration from the start of treatment to the onset of effects and association between treatment effects and side effects

In our study, epileptic seizures were completely suppressed in 37 cases and we judged that ACTH therapy was effective in these cases. In 4 cases, epileptic seizures were not completely suppressed, whereas in the other 2 cases, clinical manifestation of epileptic seizures was not obvious and we could not evaluate the efficacy of ACTH therapy. In our study, the mean duration from the start of treatment to seizure suppression for the 37 cases was 10 days. We compared the frequency of the side effects between the group effectively treated with ACTH therapy and the group whose epileptic seizures were not effectively treated with ACTH therapy (Table 3). All cases had brain shrinkage, except for 1 case with severe brain atrophy before the therapy. Hypertension was also found in most of the cases. The ACTH therapy was effective for all 7 patients who underwent abdominal CT examination.

Discussion

We found remarkable changes in the urinary Ca and P levels within 2 weeks after initiating ACTH therapy. ACTH stimulates parathormone (PTH) as well as cortisol [3, 9]. Cortisol can increase urinary Ca/Cr and P/Cr ratio by decreasing %TRCa and %TRP. PTH reduces urinary Ca/Cr ratio and increases urinary P/Cr ratio by increasing %TRCa and decreasing %TRP [3, 9]. From these facts, our data imply that PTH mainly causes the urinary changes in Ca or P in the first several days after initiating ACTH therapy, and the influence of cortisol becomes apparent after 2 weeks of treatment. Furthermore, urinary dilution by the increased fluid intake also affects the urinary data, and urinary Ca and P levels were not increased during the therapy compared to their values before treatment.

Although the effect of ACTH on urinary pH has not been previously reported, urinary pH gradually increased up to approximately 7.5 within one week of therapy in our study. Previously, patients treated with ZNS or TPM combined with ACTH therapy had alkaline urine because of the carbonic anhydrase effect of ZNS or TPM [1, 2, 10]. However, we did not use these drugs during ACTH therapy. ACTH can affect urinary pH by various mechanisms. Besides cortisol, aldosterone secretion is also stimulated by ACTH [11], and these hormones can increase the urinary pH [12-14]. Given that the urinary pH after meals increases [6], the increased appetite during ACTH therapy is one

of these mechanisms. Hyperventilation caused by mood disturbance during treatment can also cause urine alkalinity [15].

Although 93% of the patients had no findings in the urinary sediment before ACTH therapy in our study, urinary crystals or RTECs were frequently found in most of the patients during therapy. Renal tubular injury by crystals is suspected to have caused these findings in the urinary sediment [6, 7] Furthermore, our findings of ECs or hematuria in some of the patients are consistent with the findings of renal tubular injury caused by calcified lesions or its precursor lesions [6, 7]. In the patients who underwent CT, ECs or hematuria preceded by urinary crystals or RTECs were found only in patients with calcified lesions. Sequential changes in the urinary sediment from crystals or RTECs to ECs or hematuria may reflect the process of calcified lesion formation. This process involves a transition from Randall's plugs to calcified lesions by substituting the epithelial cells of the renal tubule [5-7]. Our data suggest that calcified lesions should be suspected in patients especially with ECs or hematuria during ACTH therapy. ECs or hematuria, in addition to other side effects, were not associated with the effectivity of the treatment in our study.

We found that Ca concentrations in the urine during ACTH therapy were significantly higher in the cases with ECs or hematuria than in the cases without these

findings. Although urinary Ca/Cr ratio is thought to be important when evaluating the risk of Ca-related stones [16], this parameter was not significantly different between the 2 groups in our study. Generally, crystals are formed when the solubility of salts exceeds a threshold, and pH or salt concentrations have a significant influence on this threshold [6, 17]. This indicates the importance of urinary Ca concentrations in the formation of calcified lesions. However, we believe that urinary Ca/Cr ratio is also important, because urinary Ca/Cr ratio indicates daily Ca excretion [18, 19]. Adequate fluid intake is required for both patients with high urinary Ca levels and those with high urinary Ca/Cr ratio to prevent calcified lesion formation. Except for urinary Ca concentrations, proteinuria, frequency of urinary crystals, and the number of RTECs in the urinary sediment were different between the 2 groups. Frequent urinary crystals suggest calcified lesions, whereas occasional urinary crystals can be found in normal infants [20]. The presence of many RTECs in the urinary sediment indicates a high disturbance of the renal tubules [6, 7]. Previous reports showed that increased albumin concentrations contribute to cast formation [6], and proteinuria was frequently found in patients with calcified lesions [21]. These findings are consistent with our results. We speculate that patients with calcified lesions caused by ACTH therapy tend to show frequent crystalluria, proteinuria, or many RTECs in the urinary sediment besides ECs

or hematuria. Therefore, physicians need to pay attention to calcified lesions in patients with these findings during ACTH therapy.

This study had some limitations. First, the urinary samples were obtained randomly because this was a retrospective study, despite the fact that urinary sampling in the fasting state is recommended for evaluating urinary Ca. However, we frequently obtained urinary samples for every patient and in the same timeframe. Second, the underlying causes of West syndrome varied, which can influence the outcomes of this study. Third, because we did not perform abdominal CT in all of the patients, we could not diagnose the calcified lesions, except for 4 patients. Therefore, we could not precisely show the relationship between calcified lesions and ECs or hematuria in a large number of patients. Fourth, although we examined a large number of patients compared with a previous study [3], the number of patients especially with ECs or hematuria was insufficient. Fifth, because ECs or hematuria in the urinary sediment is not frequently found, some cases may not be detected. However, the possible utility of urinalysis to detect high-risk patients with calcified lesions during ACTH therapy was demonstrated in this study.

In conclusion, within 2 weeks after initiating ACTH therapy, urinary pH and Ca/Cr ratio increased and crystals can be easily formed. Detecting urinary sediments is

an easy and useful way to identify high-risk patients with renal calcified lesions during ACTH therapy.

Acknowledgments

We are grateful to the all of the staff of Okayama University Hospital who were involved in this study, especially to Dr. Fumika Endoh, Dr. Takashi Shibata, Dr. Yoshiyuki Hanaoka, Dr. Kiyohiro Kim, and Dr. Yuki Hyodo for their clinical assistance. We would like to thank Editage (<https://www.editage.jp>) for English language editing.

Disclosure statement

The authors declare no conflict of interest.

Author contribution

H.M., K.H., and H.T. designed the study; H.M., T.A., M.A., M.O., and K.K. collected and analyzed data; H.M., T.A., K.H., M.A., and M.O. wrote the manuscript, T.A., K.H., K.K., and H.T. gave conceptual advice. All authors read and approved the final manuscript.

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Tables

Table 1. Findings in the urinary sediment before and during the therapy

	Before (%)	During (%)
No finding	40 (93)	3 (7)
Urinary crystal	3 (7)	39 (91)
RTECs	0 (0)	33 (77)
ECs	0 (0)	12 (28)
Hematuria	0 (0)	2 (5)

RTECs, renal tubular epithelial cells; ECs, epithelial casts

Table 2. Differences in clinical characteristic between patients with (group 1) and without ECs or hematuria (group 2)

Parameter	Group 1 (n=13)	Group 2 (n=30)	P-value
	Median (min-max) or n (%)	Median (min-max) or n (%)	
Age (months)	7 (5-23)	8 (3-24)	0.18
Sex, male (%)	7 (53)	16 (53)	1.0 [†]
SD score of BMI	-0.28 (-2.5-1.2)	-0.02 (-2.2-2.4)	0.34
Frequency of urinalysis during treatment	10 (8-13)	10 (6-12)	0.19
Mean serum Ca during treatment (mg/dL)	9.8 (8.5-10.1)	9.7 (8.9-10.6)	0.6
Mean serum P during treatment (mg/dL)	3.7 (3.1-4.6)	4.1 (3.0-5.4)	0.14
Mean urinary Ca during treatment (mg/dL)	8.7 (5.4-16.5)	6.2 (3.1-11.1)	0.013*
Mean urinary Ca/Cr ratio during treatment (mg/dL)	0.6 (0.3-10.0)	0.6 (0.3-15.0)	0.63
Mean urinary P during treatment (mg/dL)	20.7 (8.1-46.7)	16.8 (9.1-68)	0.27
Mean urinary pH during treatment	7.4 (6.9-7.8)	7.5 (6.7-7.7)	1.0
Proteinuria during treatment (%)	9 (69)	7 (23)	0.007 [†] *
Glucosuria during treatment (%)	5 (39)	15 (50)	0.53 [†]
Pyuria during treatment (%)	8 (62)	12 (40)	0.32 [†]
Frequency of crystals in urinary sediment during treatment	4 (2-8)	2 (0-8)	0.038*
Frequency of RTECs in urinary sediment during treatment			
1-4/HPF	1 (0-4)	1 (0-6)	0.54
5-9/HPF	1 (0-3)	0 (0-2)	0.028*

10-19/HPF	1 (0-3)	0 (0-1)	0.001*
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* $P < 0.050$.

† P values are for the Fisher's exact test.

P values are for Mann–Whitney U-test unless otherwise indicated.

SD, standard deviation; BMI, body mass index; HPF, high-power field; Ca, calcium; P, phosphate, Cr, creatinine; RTECs, renal tubular epithelial cells

Table 3. Relation between complication and effectivity of ACTH administration

	Complication n (%)				
	Hematuria or ECs in urinary sediment	Irritation	Hypokalemia	Hypertension	Brain shrinkage
Effective group (n=37)	12 (32)	34 (92)	28 (76)	36 (97)	36 (97)
Non-effective group (n=4)	1 (25)	4 (100)	4 (100)	4 (100)	4 (100)
<i>P</i>-value	1.0	0.25	0.56	1.0	1.0

P-values are for the Fisher's exact test.

ECs, epithelial casts

Figure legends

Fig. 1

Changes in fluid intake, urinary volume, and laboratory data, including Ca and P levels, before and during the 30-day treatment. All data are shown as mean \pm standard error, and the minimum to maximum numbers of cases are also shown.

Fig. 2

Findings in the urinary sediment during ACTH therapy in patients with or without renal calcified lesions as diagnosed by abdominal CT. Cases 1 to 4 were diagnosed as having calcified lesions, whereas cases 5, 6, and 7 did not have calcified lesions. Cases 1 to 4 and cases 5 to 7 were separated by a dotted line.