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Evaluation of the Short-Term Effects on Bone Mineral Metabolism and the Adrenal Pathway of Adrenocorticotropic Hormone Therapy Used in Epileptic Encephalopathy

Epileptik Ensefalopatide Kullanılan Adrenokortikotropik Hormonun Kemik Mineral Metabolizması ve Adrenal Yolak Üzerine Kısa Dönem Etkilerinin Değerlendirilmesi

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Abstract

Aim: We aimed to investigate the short-term effects of adrenocorticotropic hormone (ACTH) treatment on the adrenal pathway and bone metabolism in patients with epileptic encephalopathy.

Material and Method: Two groups with 16 patients and 16 controls were formed. Before the treatment, all patients and controls were tested for bone and adrenal metabolism. Twenty doses of ACTH therapy were given to the patient group over 3 months. The tests on the patient group were repeated 1 month after the end of the treatment.

Results: In the patient group, serum calcium, phosphorus and parathyroid hormone levels increased significantly after treatment compared with before treatment. Comparing the bone metabolism of the patient and control groups, urinary calcium/creatinine ratio was higher before treatment; serum phosphorus level, bone-specific alkaline phosphatase level and the urinary calcium/creatinine ratio were higher after treatment in the patient group. In the evaluation of the adrenal pathway, no significant differences were found between fasting serum glucose, sodium, potassium, cortisol and ACTH levels before and after treatment and in the comparison of the patient and control groups.

Conclusion: Our study investigated the short-term effect of ACTH on the adrenal pathway and bone metabolism. The results show that ACTH treatment did not have a negative effect on the adrenal pathway in the early period but, its effects on bone metabolism have not been adequately clarified.

Keywords: Epileptic encephalopathy, West syndrome, adrenocorticotropic hormone

Mesut Güngör and bengü Altınordu contributed equally to the study.

Öz

Amaç: Epileptik ensefalopatili hastalarda adrenokortikotropik hormon (ACTH) tedavisinin adrenal yolak ve kemik metabolizması üzerine kısa dönemli etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: 16 hasta ve 16 kontrolden oluşan iki grup oluşturuldu. Tedavi öncesi tüm hasta ve kontrollere kemik ve adrenal metabolizma testleri yapıldı. Hasta grubuna 3 ay boyunca 20 doz ACTH tedavisi verildi. Hasta grubundaki testler tedavi bitiminden 1 ay sonra tekrarlandı.

Bulgular: Hasta grubunda tedavi öncesine göre tedavi sonrası serum kalsiyum, fosfor ve paratiroid hormon düzeyleri anlamlı olarak yükseldi. Hasta ve kontrol gruplarının kemik metabolizması karşılaştırıldığında, tedavi öncesi idrar kalsiyum/kreatinin oranı daha yüksekti; hasta grubunda tedavi sonrası serum fosfor düzeyi, kemiğe özgü alkalin fosfataz düzeyi ve idrar kalsiyum/kreatinin oranı daha yüksekti. Adrenal yolun değerlendirilmesinde, tedavi öncesi ve sonrası açlık serum glukozu, sodyum, potasyum, kortizol ve ACTH düzeyleri arasında ve hasta ve kontrol grupları karşılaştırıldığında anlamlı fark bulunmadı.

Sonuç: Çalışmamız ACTH'nin adrenal yol ve kemik metabolizması üzerindeki kısa vadeli etkisini araştırdı. Sonuçlar, ACTH tedavisinin erken dönemde adrenal yolak üzerinde olumsuz bir etkisinin olmadığını ancak kemik metabolizması üzerindeki etkilerinin yeterince aydınlatılmadığını göstermektedir.

Anahtar Kelimeler: Epileptik ensefalopati, West sendromu, adrenokortikotropik hormon

Mesut Güngör ve Bengü Altınordu çalışmaya eşit oranda katkıda bulunmuştur

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INTRODUCTION

Epileptic encephalopathy is a group of diseases and epileptic syndromes, that epileptic activity itself cause severe cognitive and behavioral disorders, beyond what is expected from the underlying pathology (such as cortical malformation) accompanied by epileptiform electroencephalography (EEG) changes.[1] Conventional antiepileptic drugs, immunomodulatory treatments (steroids, intravenous immunoglobulin, plasmapheresis, etc.), ketogenic diet or surgical treatments have been tried in the treatment of these patients.[1,2]

Adrenocorticotropic hormone (ACTH) is a treatment option shown to have short-term efficacy in epileptic encephalopathy.[3] Although its exact mechanism of action is not known, it is suggested that it reduces neuronal hyper-excitability by suppressing corticotropin-releasing hormone (CRH) metabolism and secretion and suppresses seizures with this mechanism. Side effects of ACTH treatment such as weight gain, hypertension, restlessness, and infection have been reported.[4,5] There are limited data in the literature regarding the effects of ACTH on the steroid-dependent adrenal pathway and bone metabolism.

In our study, we aimed to investigate the short-term effects of ACTH treatment on the adrenal pathway and bone metabolism in patients with epileptic encephalopathy.

MATERIAL AND METHOD

The study was carried out with the permission of Kocaeli University Clinical Research Ethics Committee (Date: 09.04.2013, Decision No: 8/16). Every patient who was diagnosed with epileptic encephalopathy in our clinic and who was scheduled for ACTH treatment due to insufficient response to antiepileptic medication was included in the study. Exclusion criteria included previous ACTH treatment, systemic disease-causing adrenal pathway involvement other than epileptic encephalopathy and bone metabolism disorders.

We aimed to investigate the effect of ACTH treatment on the adrenal pathway and bone metabolism in the short term by performing tests on the patients in the study group before and after treatment. A control group consisted 16 children with a diagnosis of idiopathic or familial epilepsy, no mental or motor development retardation, no other systemic disease and receiving conventional antiepileptic treatment for at least 3 months. After obtaining family consent for these children, tests on the adrenal pathway and bone metabolism were performed on the children in the patient group according to the same protocol and in the same laboratory.

To evaluate the bone metabolism of the children in the patient group, determinants such as whether they received vitamin D supplements, level of sun exposure, and the degree of mobility were recorded by asking their families. Before treatment, serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-OH vitamin D level, serum C-terminal collagen (CTx), osteocalcin, bone-specific alkaline phosphatase, urinary calcium and creatinine (in 3 different spot urine samples), renal ultrasonography examinations were performed. For evaluation of the adrenal pathway, the patients and children in the control group were invited to the hospital and serum fasting glucose, sodium, potassium, cortisol and ACTH values were measured at 08:00 hours. If the serum cortisol level was below 10 µg/dl, the basal cortisol test was repeated at the same time on another day. A low-dose ACTH stimulation test was performed to exclude adrenal insufficiency in children with control serum cortisol levels below 10 µg/dl. In the patient group, synthetic ACTH was administered intramuscularly at a dose of 0.035 mg/kg, giving a total of 20 doses over a 3-month treatment period. One month after the ACTH treatment was finished, the tests were repeated, except for 25-OH-D vitamin. Only baseline evaluations were done in children in the control group, and unlike children in the patient group, renal ultrasonography was not performed in children in this group.

The Statistical Package for Social Sciences (SPSS) program was used for the statistical evaluation of the data. Continuous variables are expressed as the mean±standard deviation and frequency data are expressed as number (%). A P value <0.05 was regarded as statistically significant.

RESULTS

Among 19 patients who were followed up in our clinic with a diagnosis of epileptic encephalopathy and were indicated for ACTH treatment, 16 children who met the inclusion criteria were included in the study. Seven (43.75%) were girls and 9 (56.25%) were boys. One of the patients died of unknown cause during the study.

The mean age of the patients was 2.86±1.86 (range 0.7–7 years) years. Twelve children (75%) were being followed up due to West syndrome. Two thirds of the patients diagnosed with West syndrome were in the symptomatic group (8 cases), and one third (4 cases) were in the cryptogenic group. Distribution by age, evaluation of the cause, degree of sun exposure and mobilization status in the sick children in the study group are summarized in **Table 1**.

Fourteen of the patients (87.5%) received vitamin D supplements in their infancy; none received calcium or phosphorus supplements. Eight (50%) of the patients were exposed to enough sun every day. It was observed that 13 (81.25%) patients preferred the closed clothing style of their mothers and 3 (18.75%) preferred the open clothing style of their mothers. Eight (50%) of the patients were bedridden; 5 (31.25%) could walk without assistance.

In the examinations performed to evaluate bone metabolism before ACTH treatment in the patient group, the Ca, P, ALP, PTH levels of all patients were within normal limits. Serum CTx, osteocalcin and bone-specific ALP could be measured in

only 3 patients before ACTH treatment. Serum CTx in one of these patients, bone-specific ALP in 2, and osteocalcin in one patient were above normal limits for age. The relationship between serum CTx, bone-specific ALP or osteocalcin levels of the patients with a history of vitamin D supplementation during pregnancy, a history of vitamin D supplementation, the mother's dressing style, degree of mobility or sun exposure were not found to be statistically significant. The tests performed to evaluate the bone metabolism and adrenal pathway before and after ACTH treatment are shown in **Table 2**.

Table 1. Classification of the patient group in terms of distribution by age, cause, duration of sun exposure and mobility

Diagnosis	Number of patients	Percentage
Distribution by age		
Age range of the patients		
0–1 years	6	37.50
1–2 years	3	18.75
2–3 years	2	12.50
3–4 years	2	12.50
4–5 years	2	12.50
6–7 years	1	6.25
Total	16	100.00
Distribution by cause		
Preparatory cause		
West syndrome	12	75.00
Cryptogenic	4	25.00
Symptomatic	8	50.00
Periventricular leukomalacia	2	
Genetic	1	
Hypoglycemic sequela	1	
Pseudo-TORCH syndrome/hydrocephalus	1	
Traumatic brain injury	1	
Structural brain anomaly	1	
Sturge-Weber syndrome	1	
Congenital metabolic disease: mitochondrial disease	1	6.25
ESES: Rolandic epilepsy	1	6.25
Focal ESES: Herpes simplex encephalitis sequela	1	6.25
Myoclonic astatic epilepsy	1	6.25
Total	16	100.00
Patients' exposure to the sun		
Every day	8	50.00
>3 days a week	3	18.75
<3 days a week	2	12.50
Rarely	3	18.75
Total	16	100.00
Degree of mobility		
Bedridden	8	50.00
Unable to walk without help, but not confined to bed	3	18.75
Able to walk without help	5	31.25
Total	16	100.00

Abbreviation: ESES, electrical status epilepticus in sleep.

Table 2. Comparison of biochemical markers related to bone metabolism and the adrenal pathway in patients with epileptic encephalopathy before and after ACTH treatment

	Before ACTH treatment	After ACTH treatment	P value
Markers of bone metabolism			
Serum Ca (mg/dl)	9.52±0.29	9.85±0.46	0.03
Serum P (mg/dl)	5.10±0.78	5.90±0.73	0.004
Serum ALP (u/L)	197±104	217±60	0.20
Serum PTH (pm/L)	22.80±2.58	29.88±2.82	0.003
Serum CTx (ng/ml)	1.65±0.43	2.47±0.74	0.16*
Serum osteocalcin (ng/ml)	91.16±13.09	93.80±8.70	0.60*
Urinary Ca/creatinine	0.24±0.17	0.17±0.13	0.12
Biochemical markers related to the adrenal pathway			
Serum glucose (mg/dl)	82.6±9.7	88.8±27.3	0.43
Serum Na (mEq/L)	138.5±2.6	138.6±1.9	0.92
Serum K (mEq/L)	4.57±0.56	4.67±0.42	0.59
Serum cortisol (µg/dl)	12.9±5	11.0±4.0	0.12
Serum ACTH (pg/ml)	24.2±11.2	24.4±8.5	0.99

P values <0.05 are statistically significant. Abbreviations: ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; PTH, parathyroid hormone; CTx, C-terminal collagen. *Evaluation was possible in 3 patients before treatment.

In the pre-treatment renal ultrasonography, 11 (78.6%) patients were found to be normal, 2 had (14.3%) nephrolithiasis and 1 (7.1%) was suspicious for nephrolithiasis. No statistically significant correlation was found between ultrasonographic findings and serum Ca, P, ALP, PTH levels or urinary Ca/creatinine ratio. There was no significant difference between the evaluations made by renal ultrasonography in terms of nephrolithiasis before and after treatment (P> 0.05).

The serum 25-OH vitamin D level was below 20 ng/ml in 4 patients in the pre-treatment patient group. No statistically significant correlation was found between the 25-OH vitamin D level of the patients and variables such as whether they received vitamin D supplementation, the degree of mobility, whether the mother took vitamin D during pregnancy, the mother's dressing style or sun exposure (P> 0.05).

When the characteristics of bone metabolism of the patients who received ACTH treatment were compared before and after the treatment, a significant increase was observed in serum Ca, P and PTH levels (P< 0.05), but no significant difference was found in the serum ALP level and urinary Ca/creatinine ratio (**Table 2**). The values for serum CTx, bone-specific ALP and osteocalcin levels were measured in only 3 patients in the pre-treatment period, therefore statistical evaluation could not be done. After ACTH treatment, CTx, bone-specific ALP and osteocalcin levels were observed to be above normal limits in 6 patients.

When the characteristics of the adrenal pathway of the patients who received ACTH treatment were compared before and after the treatment, no significant difference was found in the fasting glucose, Na, K, cortisol, ACTH tests (P> 0.05). A low-dose ACTH stimulation test was performed because basal cortisol values in 2 patients before treatment and 3 patients after treatment were below 10 µg/dl. In these cases, adrenal insufficiency was excluded by finding adequate cortisol responses after the ACTH stimulation test.

The biochemical markers related to bone metabolism and the adrenal pathway of the patient group with epileptic encephalopathy before and after ACTH treatment are compared with the control group in **Table 3**.

Tablo 3. Biochemical markers related to bone metabolism and the adrenal pathway in patients with epileptic encephalopathy before and after ACTH treatment compared with the control group

Biochemical marker	Patient group	Control group	P value
Before treatment			
Bone metabolism			
Serum P (mg/dl)	5.03±0.75	5.2±0.51	0.09
Serum ALP (u/L)	190.4±98.0	227±72	0.25
Serum PTH (pm/L)	25.0±11.9	29±11	0.73
Serum 25-OH-Vit D	29.8±15.6	26.7±9.9	0.26
Urinary Ca/creatinine	0.23±0.16	0.06±0.70	0.02
Serum CTx (ng/ml)	1.65±0.43	2.17±0.54	0.59
Serum bone-specific ALP (µg/dl)	87.20±4.77	70.4±12.7	0.16
Serum osteocalcin (ng/ml)	91.1±13.9	72.2±20.8	0.32
Adrenal pathway			
Serum glucose (mg/dl)	82.0±9.5	78.8±12.3	0.98
Serum Na (mEq/L)	138.4±2.6	137.0±2.3	0.84
Serum K (mEq/L)	4.5±0.5	4.7±0.52	0.15
Serum cortisol (µg/dl)	13.0±4.8	12.0±2.7	0.08
Serum ACTH (pg/ml)	23.0±10.9	28.6±12.7	0.79
After treatment			
Bone metabolism			
Serum Ca (mg/dl)	9.85±0.46	9.85±0.49	1.00
Serum P (mg/dl)	5.90±0.73	5.24±0.51	0.01
Serum ALP (u/L)	217.0±60.4	227.0±72.3	0.68
Serum PTH (pm/L)	29.8±10.5	29.3±11.2	0.90
Urinary Ca/creatinine	0.15±0.12	0.06±0.07	0.04
Serum CTx (ng/ml)	2.09±0.59	2.17±0.54	0.69
Serum bone-specific ALP (µg/dl)	82.7±11.8	70.4±12.7	0.03
Serum osteocalcin (ng/ml)	62.2±24.1	72.2±20.8	0.24
Adrenal pathway			
Serum glucose (mg/dl)	88.8±28.3	78.8±12.3	0.21
Serum Na (mEq/L)	138.60±1.99	137.25±2.35	0.10
Serum K (mEq/L)	4.67±0.42	4.70±0.52	0.90
Serum cortisol (µg/dl)	11.04±4.87	12.33±2.56	0.36
Serum ACTH (pg/ml)	24.26±8.55	28.6±12.7	0.28

P values <0.05 are statistically significant. Abbreviations: ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; PTH, parathyroid hormone; CTx, C-terminal collagen.

When the bone metabolism tests of the children in the patient group before ACTH treatment were compared with the basal tests of the children in the control group, no significant differences were found between the 2 groups except for the urinary Ca/creatinine ratio. The urinary Ca/creatinine ratio was found to be significantly higher in patients with epileptic encephalopathy compared with the control group. When the results of bone metabolism tests for the patients after ACTH treatment were compared with the results for the control group, serum P and bone-specific ALP values and the urinary Ca/creatinine ratio were found to be significantly higher in the patients who received ACTH treatment (P< 0.05).

In the comparison of the basal test results performed for the adrenal pathway in the control group and the results related to the adrenal pathway both before and after treatment in the patient group (**Table 3**), no significant differences were found between the 2 groups (P> 0.05).

DISCUSSION

ACTH is generally the first treatment option for epileptic encephalopathy. Although some studies have reported that ACTH treatment can be applied safely, there is not enough information in the literature about the effect of ACTH on the short-term adrenal pathway and bone metabolism. In our study, 16 patients with a diagnosis of epileptic encephalopathy who received an indication for ACTH treatment were followed prospectively. The aim was to investigate the short-term effect of ACTH treatment by comparing bone metabolism and adrenal pathway functions in the patient group before and early after treatment.

Considering the age characteristics of the patient group, most of the children were between 0 and 3 years of age (11; 68.75%). More than half of these patients (6; 37.5%) were in infancy. The concentration of patients in the first 3 years was associated with the fact that most cases (12; 75%) were diagnosed with West syndrome and this syndrome is observed more frequently in the first 2 years of life. Two thirds of the patients diagnosed with West syndrome were in the symptomatic group,[8] and one third[4] were in the cryptogenic group. The higher number of patients in the symptomatic group was attributed to the advances in diagnostic laboratory examinations in recent years and was consistent with the literature.[6]

The source of vitamin D in infancy is transplacental transmission from the mother, breast milk and sunlight. The serum 25-OH vitamin D level of the patients in the study group was below 20 ng/ml in 4 patients participating in the study. Contrary to what was expected, no statistically significant relationship was found between the 25-OH vitamin D level of these patients and patient-dependent factors such as whether they received vitamin D prophylaxis, degree of mobility or sun exposure, as well as maternal variables such as whether the mother took vitamin D during pregnancy or the mother's dressing style. In a study investigating the vitamin D level in infants and the factors affecting this level, Özdemir et al.[7] found that the vitamin D level was associated with the mother's dressing style, the baby given vitamin D prophylaxis at the recommended dose and duration, and adequate exposure to sunlight. In our study, no statistically significant relationship was found between vitamin D and these variables. The reason why this relationship could not be determined may be related to the small number of cases and the small number of mothers [3] who prefer an open dressing style.

The importance of physical activity and immobilization in bone metabolism and its relationship with secondary osteopenia is known.[8] Eight (50%) of the patients in the study group were bedridden, 5 (31.25%) could walk unaided and 3 (18.75%) could walk with assistance. There was no difference between the 3 groups in terms of the degree of immobility and serum Ca, P, ALP, PTH or serum vitamin D levels. Taşdemir et al.[9] reported immobilization as an important variable on bone mineral density and bone metabolism markers in their study on 24 patients with mobile and immobile cerebral palsy and a control group. In our study, no significant relationship was found between immobilization and bone metabolism markers. This may be due to the shorter immobilization times than the studies in the literature and the small number of patients and their young age.

Epidemiological studies show that the risk of osteoporotic fractures increases depending on the glucocorticoid dose.[10] It has been shown that glucocorticoids used in congenital adrenal hyperplasia and primary adrenal insufficiency at physiological doses have no effect on bone mineral density.[11] However, the effect of standard ACTH treatment on glucocorticoids and bone metabolism is controversial. In our study group, the serum Ca, P and PTH values, which were measured to evaluate bone metabolism, increased statistically significantly after treatment compared with before treatment. Although the P and PTH values remained within normal limits, the Ca value was found to be above the normal limit in 4 patients. In addition to the increase in mean serum Ca levels after treatment, hypercalcemia was observed in 1 of every 4 patients, suggesting that ACTH treatment has an effect on Ca metabolism in the short term. Although ACTH treatment causes an increase in cortisol, there may be adrenal suppression and temporary cortisol insufficiency as a result of prolonged negative feedback during the treatment process. In the case of cortisol insufficiency, Ca absorption from the intestines increases and hypercalcemia may develop. As observed in our patients, the short-term effects of ACTH treatment on Ca and P mineral metabolism and on bone health in the long term should be evaluated clinically. Consistent with our results, Riikonen et al.[12] showed a statistically significant increase in mean serum Ca and P levels after ACTH treatment. However, they showed that these biochemical changes are reversible and therefore reported that short-term ACTH treatment may not lead to permanent changes in bone metabolism.

It is known that glucocorticoids cause hypercalciuria and urinary Ca excretion returns to normal after treatment. Düzen et al.[13] showed that there was no significant change in serum Ca, P, ALP, PTH levels in 42 patients who received low-dose glucocorticoids before and after treatment; urinary Ca excretion increased during treatment, but returned to normal after treatment cessation. In a study evaluating the development of hypercalciuria with ACTH treatment, it was shown that urinary calcium excretion increased statistically significantly after ACTH treatment and this returned to normal at the end of the first month. In their studies evaluating bone metabolism in children with nephrotic syndrome who received glucocorticoid treatment, Koşan et al.[14] showed that the urinary Ca/creatinine ratio measured before treatment was increased significantly at the 4th and 12th weeks of the treatment. Our results do not support this finding and the decrease in urinary Ca excretion after ACTH treatment, although noteworthy, was not statistically significant in our cases. Our findings suggest that hypercalciuria is not an important complication of ACTH treatment.

There are results showing that hypercalciuria due to increased cortisol caused by ACTH may result in renal calcification. Secondary hyperparathyroidism, hypercalcemia, hyperphosphatemia and metabolic alkalosis are thought to predispose to this situation. ACTH or glucocorticoids are known to increase glomerular filtration, disrupt tubular function, and cause hypercalciuria and nephrolithiasis.[15] In our study, nephrolithiasis was detected in 2 of the patients in the period before treatment with ACTH was initiated, and both patients had significant hypercalciuria. It was thought that calcium imbalance disorder in the baseline evaluation of these patients might be due to metabolic processes related to the underlying primary diseases. When all cases were evaluated, no significant difference was found in terms of hypercalciuria and nephrolithiasis in the period after ACTH treatment. Although Riikonnen et al.[12] reported an increase in the rate of nephrolithiasis in a postmortem study of children who received ACTH treatment, it is not possible to establish a direct relationship between ACTH treatment and nephrolithiasis, because various risk factors such as immobilization and malnutrition may accompany the risk of stone formation in children receiving ACTH treatment. In our study, a statistically significant increase in nephrolithiasis before and after treatment in patients who received ACTH and in hypercalciuria could not be demonstrated in the patients who developed suspicious nephrolithiasis after treatment. Nevertheless, due to the small size of our patient group, it would be appropriate to follow up patients who received ACTH therapy in terms of nephrolithiasis until more comprehensive study results are available.

There is no study in the literature investigating the effect of ACTH treatment on bone mineral metabolism with bone turnover markers. It is thought that the effects of ACTH on bone are due to the increase in glucocorticoid. Glucocorticoids suppress osteoblastic activity in bone and increase bone resorption. Kruse et al.[16] evaluated bone metabolism in 11 patients who previously received dexamethasone, prednisolone or ACTH, and showed that serum ALP, osteocalcin and urine hydroxyproline levels decreased, and glucocorticoids decreased osteoblastic

activity and increased osteoclastic activity. We planned to evaluate serum CTx, bone-specific alkaline phosphatase and osteocalcin levels, parameters of bone turnover before the treatment, but these markers could be measured in only 3 patients for technical reasons at the time of the study. Although the CTx level was normal before treatment in 1 of the patients, it was above the normal limit after treatment. After the treatment, the osteocalcin level was normal. In our study group, in contrast to Kruse et al.[16] ACTH treatment significantly increased the level of bone-specific alkaline phosphatase in children whose bone turnover parameters were measured in the post-treatment period compared with children in the control group. It is known that the effects of glucocorticoids on ALP may be different in vivo and in vitro, decreasing ALP in in vivo conditions and increasing the production of ALP in in vitro conditions.[17] Although an increase in bone-specific ALP, increase in CTx and decrease in osteocalcin could not be shown in our study group, it suggests that bone formation was stimulated. Whether this increase in bone formation is temporary or permanent would require further follow-up of the patients.

ACTH treatment may cause adrenal insufficiency by suppressing CRH and ACTH production in children. The risk of adrenal insufficiency may vary according to the daily dose and duration of plasma ACTH suppression.[18] In our study, we aimed to investigate whether standard ACTH therapy exerts pressure on the adrenal gland in the short term. In our patient group, there were no significant differences between the adrenal pathway evaluations before and after ACTH treatment. Similarly, the adrenal pathway evaluations in our control group did not differ significantly with both the pre-treatment and post-treatment evaluations in our patient group. These findings show that standard ACTH therapy does not cause adrenal suppression in the early period. It is known that suppression of the adrenal pathway caused by glucocorticoid therapy may vary from person to person, and the pathway can spontaneously return to normal between 3 weeks and 6 months after cessation of treatment. Perheentupa et al.[19] evaluated the adrenal pathway in the first days after the treatment, and we deemed it appropriate to perform the adrenal pathway evaluation 1 month after the treatment. The results of the 2 evaluations were different in terms of adrenal pathway suppression, which may be related to the time after treatment. Assessment of the adrenal pathway is difficult due to the diurnal release of cortisol and the possibility of changes in this release due to ACTH treatment. In our study, obtaining a sufficient adrenal response to the low-dose ACTH stimulation test in patients with low cortisol 1 month after the ACTH treatment suggested that possible short-term adrenal suppression disappeared at the end of 1 month at the latest, even during the treatment process. In conclusion, we believe that there is no need for routine adrenal pathway evaluation in children receiving standard ACTH therapy.

CONCLUSION

Although ACTH treatment is often used as the first option in the treatment of epileptic encephalopathy, there is not enough information about its short-term effects on the adrenal pathway and bone metabolism. Our study was planned to investigate the short-term effects of ACTH on the adrenal pathway and bone metabolism, and according to our results, ACTH treatment does not have an early negative effect on the adrenal pathway. The effects of ACTH treatment on bone metabolism are controversial. According to the results of our study, ACTH treatment might have an effect on Ca, P mineral metabolism in the short term. Although our results suggest that bone metabolism markers may be useful in showing possible instantaneous changes in the bone formation resorption cycle during ACTH treatment, their net effects on bone health in the long term should be monitored.

In conclusion, although ACTH therapy is a reliable treatment method in terms of suppression of the adrenal pathway, its effects on bone metabolism have not been adequately clarified. New comparative studies in which patients are followed up for a long time are needed to better evaluate bone metabolism.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kocaeli University Clinical Research Ethics Committee (Date: 09.04.2013, Decision No: 8/16).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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