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A Case of Pediatric Nephrolithiasis Associated with Topiramate Treatment

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= Abstract =

Topiramate is an antiepileptic drug widely used to treat various seizures, mood disorders and migraine based on its various pharmacological mechanisms. Even though nephrolithiasis is listed as one of its side effects, there have been no cases reporting nephrolithiasis caused by use of topiramate on Korean pediatric patients. Since the use of topiramate is increasing in many patients, the possibility of nephrolithiasis after the treatment needs to be considered. Here, we report our experience in correcting neprholithiasis by simply discontinuing topiramate without administering any additional treatments.

Key Words : Topiramate, Nephrolithiasis, Antiepileptics, Side effects

Introduction

Topiramate is one of widely prescribed antiepileptic drugs because of its efficacy in treating refractory seizures[1]. Among its multiple pharmacological mechanisms of action, topiramate is a known inhibitor of the enzyme carbonic anhydrase[2]. So it can develop metabolic acidosis, hypocitraturia, and elevation of urine pH, which are risk factors of nephrolithiasis[3]. Since the use of topiramate is increasing in pediatric epilepsy patients, the possibility of drug-induced nephrolithiasis needs to be considered. However, there have been no cases reporting nephrolithiasis caused by use of topiramate on Korean pediatric patients.

Here we report a case of pediatric nephrolithiasis that was likely induced by topiramate use and corrected by simply discontinuing it. The patient was diagnosed with nephrolithiasis by kidney sonography without evidence of metabolic acidosis. Two months after discontinuance of topiramate, the nephrolithiasis disappeared on sonography without administering any additional treatments. We report our case with review of the related literatures.

Case Report

A 35 month-old boy with exacerbated seizure caused by pneumonia was admitted to Seoul National University Bundang Hospital

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(SNUBH). The patient has an uncle diagnosed with mental retardation and seizures. The boy showed decreased muscle tone and required a tube feeding from the birth. At 6 months of age, the patient visited SNUBH outpatient clinic with symptoms of developmental delay. He was prescribed with thyroid hormones under the suspicion of hypothyroidism since then. A magnetic resonance imaging taken at 15 months of age showed localized brain atrophy and delayed myelination. At 27 months of age, the patient underwent a tracheotomy after being treated for dyspnea caused by respiratory syncytial virus pneumonia in an intensive care unit setting. The patient started valporate medication to treat tonic seizures that started at 12 months of age and added topiramate to the regimen since 24 months of age to treat seizures which continued even after increased dosages of valporate. He had used topiramate with the maximum dose of 5 mg per kilogram per day. The patient was admitted at 35 months of age to treat pneumonia and seizure events.

The patient was chronically ill looking and had rough breathing sound. He was not able to neither make eye contacts nor support his own neck due to developmental delay. Even though no focal neurologic abnormalities were found, his deep tendon reflex and muscle tone was increased in all four appendages. There were no signs of fever, foamy urine, turbid urine, hematuria or discomfort during urination.

The patient's complete blood cell count showed 8,910/mm^3, 13.1 g/dL and 327,000/mm^3 in the white blood cell count, hemoglobin and platelet count respectively. A venous blood gas analysis showed a pH of 7.353, a pCO_2 of 43.2 mmHg, a PO_2 of 62.3 mmHg and bicarbonate level of 23.5 mmol/L. His electrolytes included sodium levels of 137 mmol/L, potassium levels of 4.6 mmol/L, chlorine levels of 104 mmol/L and a tCO_2 22 mmol/L. In biochemical lab work, aspartate transaminase and alanine transaminase levels were slightly elevated to 41 IU/L and 75 IU/L respectively. His total protein counts were 5.9 g/dL, albumin 3.6 g/dL, blood urea nitrogen 12 mg/dL, creatinin 0.4 mg/dL, calcium 9.2 mg/dL and phosphate 5.5 mg/dL. His urinalysis was within the normal range except for a urine pH of 7.0. On the 17th day of admission, he had a urine pH 7.5 in urinalysis and calcium 123 mg/d, magnesium 4.72 mg/d, protein 30 mg/d, oxalate 0.05 mmol/d and citrate 0.39 mmol/d in 24 hour urine collection. The rest of the urinalysis findings were normal.

During the admission process, white calcification dust was found in his diapers. To follow up with his symptoms, a kidney sonography and urinary analysis was performed. The kidney sonography showed high echogenic lesions at the upper pole of the right kidney and the lower pole of the left kidney (Fig. 1). There was also a high echogenic lesion approximately 3 mm inside his bladder. The lesion's finding was congruent with findings shown in nephrolithiasis. At this point, drug treatment changed from topiramate to levetiracetam under the suspicion of nephrolithiasis caused by topiramate. No abnormal findings were found during the follow up kidney sonography at two months(Fig. 2) and four months after discontinuing the topiramate. We experienced a case of cor-

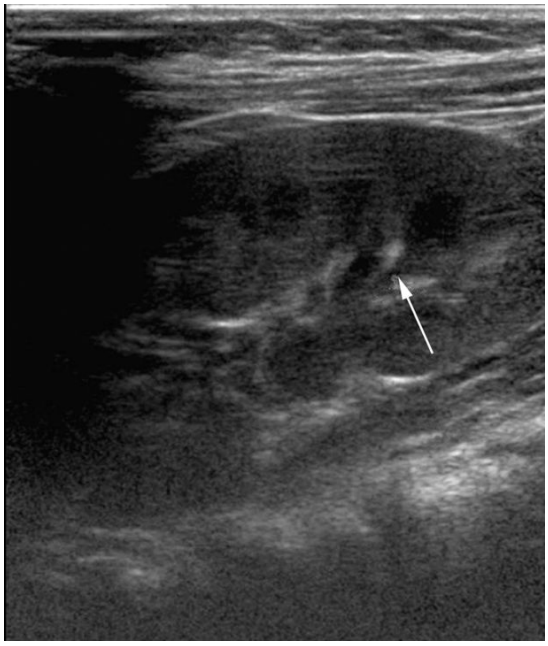

Fig. 1. A sonogram shows hyperechogenic round lesions(arrow) in the left kidney.

recting neprholithiasis by simply discontinuing topiramate without administering any additional treatments.

Discussion

Topiramate is a widely prescribed antiepileptic drug based on its multiple pharmacological actions[1]. It is used to treat a broad spectrum of multiple seizure types, including partial and generalized seizures[4, 5]. Currently, its use is not limited to just its traditional use in epilepsy patients. It is also used to treat various diseases including mood disorders, eating disorders and migraine prevention[6-8]. Other than its known side effects such as cognitive dysfunction, dysesthesia and loss of appetite, topiramate is also known for its inhibitory effects on carbonic anhydrase which may cause nephrolithiasis[3].

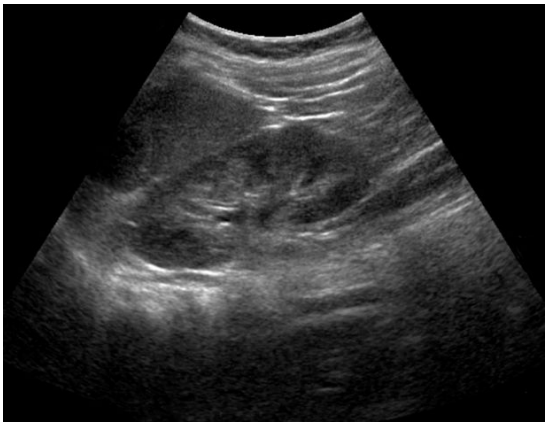

Fig. 2. A follow-up sonogram shows normal left kidney at two-months after discontinuance of topiramate.

The correlation between the inhibition of carbonic anhydrase and nephrolithiasis was first introduced by a case report of nephrolithiasis after acetazolamide use 50 years ago[9]. Although there is no long term data on the incidence rate of nephrolithiasis after the use of topiramate, the correlation between nephrolithiasis and topiramate, which has similar pharmacological effects to acetazolamide, was also previously studied. Approximately 1.5% of adult patients who underwent topiramate treatment were reported to suffer from nephrolithiasis[10]. Despite the lack of studies in the pediatrics field, 4.5% of topiramate-treated patients from 45 Italian Lenox Gastaut Syndrome patients were reported to suffer from nephrolithiasis after the topiramate treatment[11]. Considering the wide use of topiramate in various diseases, nephrolithiasis should be considered one of the important side effects in using topiramate.

Symptoms including metabolic acidosis, a decrease of urinary citrate secretion, and an increase of urinary pH are important factors

that cause the formation of kidney stones in patients treated with topiramate[12]. Inhibition of the kidney's carbonic anhydrase causes metabolic acidosis by obstructing with the absorption of bicarbonate. Chronic metabolic acidosis decreases the citrate concentration within the kidney tissues and leads to hypocituria by increasing the reabsorption of citrate in the proximal tubules[13]. Since citrate is a key factor in preventing crystallization of calcium, hypocituria may be a key factor in causing nephrolithiasis in patients treated with topiramate. However, the most important factor in kidney stone formation seems to be urine pH level. Normal kidneys maintain a urine pH within the 5.8−6.2 range and minimize the formation of kidney stones. In an increased urine pH environment, more dihydrogen phosphate ions will be converted to monohydrogen phosphate ions, thus causing the increased formation of brushite. Brushites will then be converted to the hydroxyapatite, leading to increased formation of calcium phosphate stones[3]. Such a mechanism is similar to the mechanism of proximal tubular acidosis that shows hyperchloremia, normal anion gap metabolic acidosis, high urine pH, hypercalciuria and hypocituria.

Since the use of topiramate may cause the formation of kidney stones, its treatment methods as well as identification of early findings are becoming an important issue. Alkali treatment corrects metabolic acidosis caused by proximal tubular defects by increasing citrate secretion and decreasing the calcium in a patient's urine to prevent stone formation[14]. Oral citrate is also a possible treatment option. However, there are no studies performed to evaluate the efficacy of these various treatments in preventing nephrolithiasis caused by topiramate.

In this particular case, a 35 month old patient had been treated with topiramate for 10 months. His dosage had been increased to 5 mg per kilogram per day. A kidney sonography was performed to diagnose nephrolithiasis after incidentally finding calcified dust on the patient's urine sediments. No signs of metabolic acidosis or hypocituria were present except for an increased urine pH within 7.0−7.5 range. The topiramate dosage was slowly tapered off while increasing the dosage of levetiracetam under the suspicion of nephrolithiasis caused by topiramate. After discharging topiramate, no new treatments were added to his regimen since the patient did not show any new symptoms relating to nephrolithiasis. Two months after discontinuing topiramate, the high echogenic lesion found in an earlier kidney sonography was no longer present. Unlike previous hypothesis on pathophysiology of nephrolithiasis caused by topiramate, the patient did not show any signs of metabolic acidosis or hypocituria. As soon as topiramate was discontinued to remove the cause of alkalinized urine, nephrolithiasis was corrected without any additional treatments. The patient is currently being treated with levetiracetam without any serious complications.

한 글 요 약

소아에서 토피라메이트 사용 후 발생한 신 석회화증 1례

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채종희 · 김기중 · 황용승 · 황 희

토피라메이트는 다양한 작용기전에 의해 여러 간질 질환, 기분 장애, 편두통 등에 폭넓게 사용되고 있는 항간질제로 부작용으로 신석회화증의 발생이 가능한 것으로 알려져 있으나 현재까지 국내 소아에서 토피라메이트 사용에 의한 신결석에 대한 보고는 없었다. 최근 토피라메이트의 사용 빈도가 증가하고 있으므로 향후 이 약제를 사용하는 환자에 대해 신결석의 발생 가능성에 대한 고려가 필요할 것으로 생각된다. 저자들은 토피라메이트를 10개월 이상 사용한 후 신석회화증이 발생하였고, 특별한 치료 없이 투약 중지 후 신석회화증이 교정되는 소아 환자의 사례를 경험하여 이를 보고하는 바이다.

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