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Case Report Open Access

Two Cases of Infantile Spasms Complicated by Urolithiasis Developed for a Short Period of Time during ACTH-Zonisamide Therapy

Masahiro Shiraish*, Shinobu Fukumura, Toshihide Watanabe and Kimio Minagawa

Department of Pediatrics, Hokkaido Medical Center for Child Health and Rehabilitation, Hokkaido, Japan

Abstract

A 19-month-old female and a 16-month-old male child with intractable seizures were diagnosed as infantile spasms on the basis of their symptoms, clinical courses and EEGs. Both of them were born at 23 weeks gestation. We treated them by combination therapy with adrenocorticotrophic hormone (ACTH) and zonisamide (ZNS). However, urolithiasis was confirmed by computed tomography at 10 days and 12 days, respectively, after starting the combination therapy. We need to recognize that combination therapy with ACTH and ZNS carries a high risk of development of urolithiasis, and this adverse effect can happen at an early date. Regular urinalysis should be performed during therapy with these drugs, and if the presence of urolithiasis is suspected, CT scan or renal ultrasonography should be performed.

Keywords: ACTH; Infantile spasms; Nephrocalcinosis; Urolithiasis; Zonisamide

Introduction

Zonisamide (ZNS), an antiepileptic drug that is widely used in Japan for West syndrome and infantile spasms, is sometimes used in combination with adrenocorticotrophic hormone (ACTH) therapy [1,2]. While the association between ZNS and urolithiasis is known [3], the potential side effects of ACTH therapy, urolithiasis and nephrocalcinosis, are insufficiently recognized [4,5]. Herein, we report two children who temporarily developed urolithiasis after starting combination therapy with ACTH and ZNS. Informed consent was obtained from the patients' parents before treatment.

Case 1

A 19-month-old female child experienced epileptic spasms from the age of 18 months. She was born at 23 weeks of gestation after an induced delivery because of fetal dysfunction. Her birth weight was 670 g and a five minute Apgar score was 4. She learned head control at the age of 10 months and roll over at 17 months. She was usually in a recumbent position. Before the onset of her seizures, she could smile responsively, recognize faces with no regressive episodes after seizure onset. Her seizures, which were in the form of tonic jerks of the extremities, occurred approximately five times every day, occurring periodically every few seconds and continuing for about five minutes.

On admission, she showed slightly increased muscle tonus. Routine hematological, biochemical, serological and urinary tests were normal; urinary sediments were negative. Her interictal electroencephalogram (EEG) showed intermittent diffuse polyspikes and wave discharges, with no hypsarrhythmia. To control the seizures, we initially prescribed 3 mg/kg/day ZNS, subsequently increasing it to 10 mg/kg/day (Figure 1). However, since treatment with ZNS was ineffective, ACTH, 0.0125 mg/kg/day, was added at 12 days of treatment, the drug being administered daily for two weeks without tapering. The drug combination resulted in disappearance of the seizures and improvement of the EEG. However, urinary sand and phosphate sediments appeared. Computed tomography (CT) performed 10 days after starting combination therapy confirmed the presence of urolithiasis with calcium phosphate stones (Figure 2). Therefore, ZNS was tapered and discontinued, and increased water consumption was recommended. Renal ultrasonography was performed at day 27 after ZNS therapy still confirmed the presence of urolithiasis. We checked renal ultrasonography periodically, and urolithiasis was gradually disappeared.

Case 2

A 16-month-old male, born at 23 weeks gestation because of premature rupture of membranes, experienced epileptic spasms from the age of 12 months. His birth weight was 668 g and a five minute Apgar score was 5. Since vitamin B6 (VB6) therapy had little effect, he was prescribed ZNS, 10 mg/kg/day, at the age of 13 months. His seizures, which occurred a few times every day, were temporarily controlled with ZNS, but relapsed at the age of 14 months. He had not learned head control and could not roll over at the age of 16 months. He showed increased muscle tonus, and was usually in a recumbent position. Before his seizure onset, he could smile responsively, recognize faces with no regression after seizure onset.

The patient was transferred to our hospital at 16 months of age (after 71 days of treatment with ZNS). Routine hematological, biochemical, serological and urinary tests were normal, although there were urinary phosphate sediments. Interictal EEG showed intermittent polyspikes and wave discharges in the occipital region bilaterally, with little bilateral synchrony and without hypsarrhythmia. Since ZNS monotherapy was ineffective in controlling seizure activity, ACTH therapy was added at 74 days of ZNS treatment (Figure 3), with resultant control of seizure activity and decrease in spikes and sharp waves on EEG. The dose and duration of treatment with ACTH were the same as in case 1. Although CT demonstrated no urolithiasis before therapy (Figure 3), calcium phosphate stones developed 12 days after starting combination therapy

***Corresponding author:** Masahiro Shiraishi, Department of Pediatrics, Hokkaido Medical Center for Child Health and Rehabilitation, Kanayama 1-jo, Teine-ku, Sapporo-shi, Hokkaido 006-0041, Japan, Fax: 81-11-691-1000; Tel: 81-11-691-5696; E-mail: shira_p_0420@yahoo.co.jp

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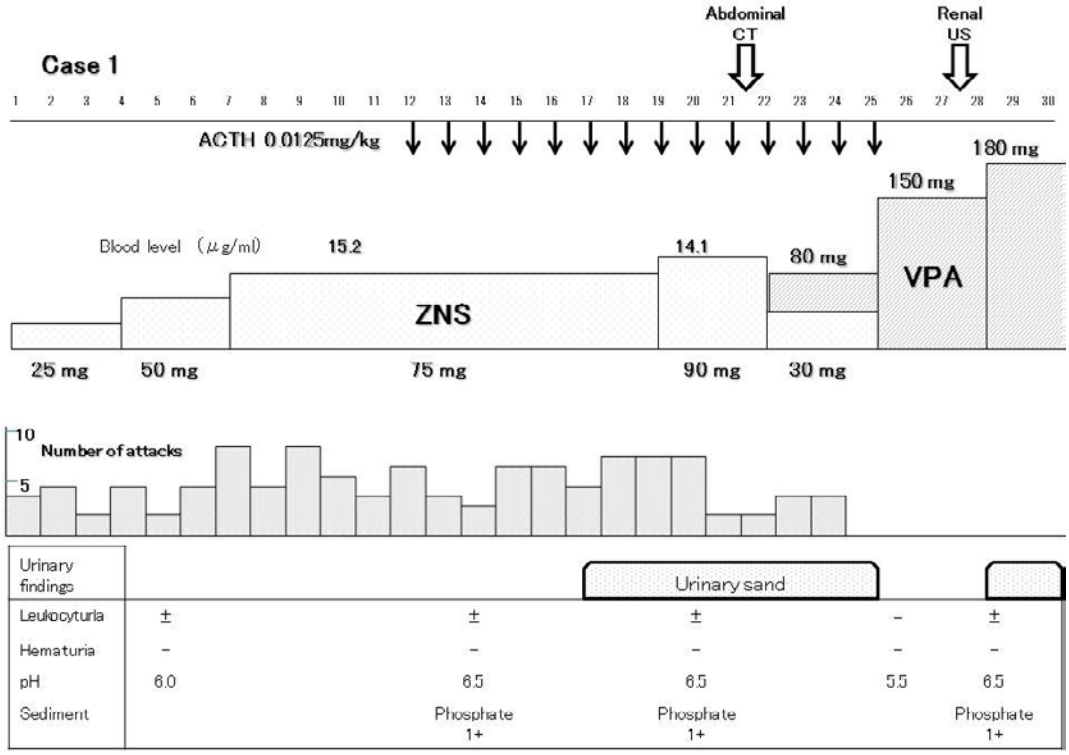

Figure 1: Time course of treatment in Case 1. The abscissa (1 to 30) denotes the number of days after starting treatment with ZNS. (CT: computed tomography; US: ultrasonography).

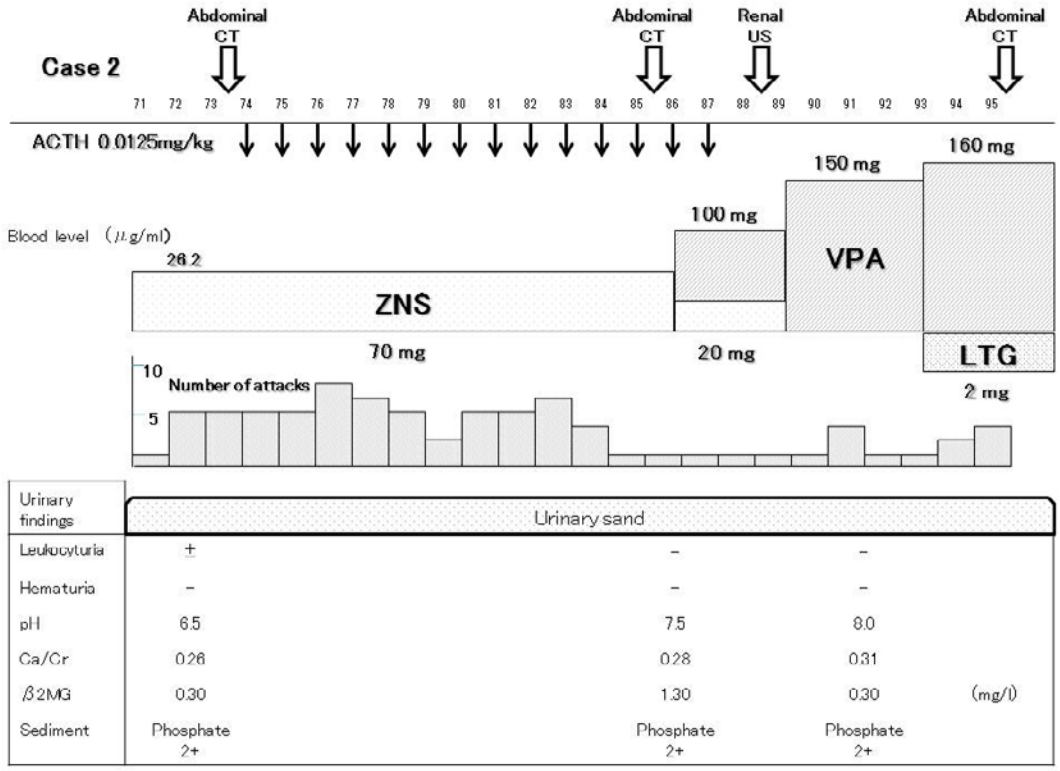

Figure 2: Time course of treatment in Case 2. The abscissa (71 to 95) denotes the number of days after starting treatment with ZNS. (CT: computed tomography; US: ultrasonography).

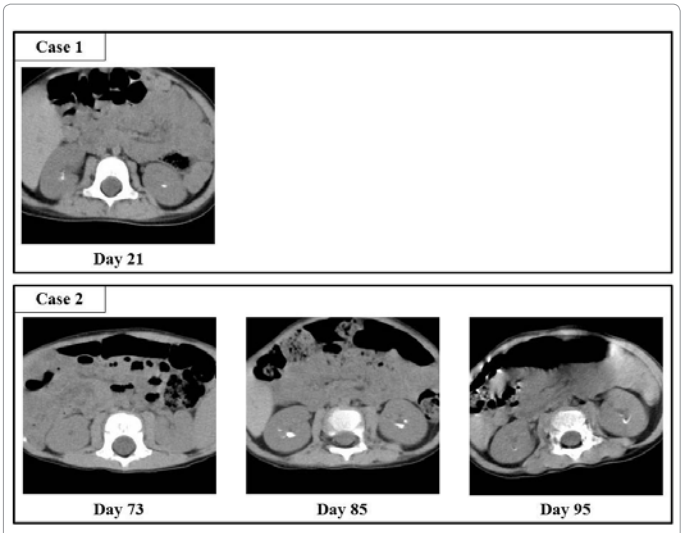

Figure 3: The number of days after starting treatment with ZNS was labeled under the picture.

(Figure 2). Hence, ZNS was discontinued. CT performed eight days after discontinuation of the combination therapy showed a decrease in the urolithiasis (Figure 2).

Discussion

The seizures in the two children reported here were compatible with the infantile spasms without hypsarrhythmia described by the West Delphi group [6]. Both our patients were refractory to ZNS monotherapy and eventually responded to combination therapy with ACTH and ZNS. ZNS should be discontinued when to start ACTH, if possible [1]. But the cases were both extremely low birth weight children, and symptomatic (not cryptogenic) patients, so we could not discontinue ZNS. Although the dosages of ZNS and ACTH used in our patients was not high compared with that used in many Japanese institutes, [2], both of our cases developed urolithiasis after starting combination therapy.

Urolithiasis and nephrocalcinosis attributed to ACTH are not sufficiently recognized. These are believed to be multifactorial in etiology, resulting from increase in urinary calcium (Ca) and phosphate (P), development of hyperparathyroidism and osteoporosis [4]. Previous studies that reported these adverse effects [4,5] used high doses of ACTH for a prolonged duration. Low-dose ACTH therapy is currently used in Japan, because complications depend on the dose and duration of treatment [2,4]. Although urolithiasis or nephrocalcinosis have not been reported with only ACTH therapy in Japan, some Japanese studies reported development of urolithiasis or nephrocalcinosis with combination ACTH and ZNS therapy [7,8]. The previously reported stones were also calcium phosphate stones, as with our patients. It is speculated that ZNS has weak carbonic anhydrase inhibitor effects, resulting in alkaline urine and increased urinary Ca excretion, which, in turn, cause urolithiasis [3,9], while ACTH may facilitate this adverse effect of ZNS by further increasing the urinary Ca [7,8]. In case 2, urinary Ca and creatinine (Cr) levels increased slightly, and urinary ß2-microglobulin increased after starting combination therapy (Figure 2). In case 1, we did not evaluate these parameters and did not check renal CT scan or ultrasonography before starting ACTH therapy, but urinary sand appeared after starting ACTH therapy, so we consider that ACTH promoting renal stone.

Urinary tract obstruction and hydronephrosis secondary to urolithiasis requires performance of invasive procedures, such as extracorporeal shock wave lithotripsy (ESWL). Hence, ZNS should be discontinued, if possible, in these patients and adequate consumption of water should be advised [7,9]. Arrabal-Martín et al. [10] reported that the administration of thiazides stabilizes or reduces the formation of residual lithiasis and favors its spontaneous elimination, since thiazides decrease urinary Ca excretion and have a diuretic effect.

Admittedly, the cases reported in this article were both extremely low birth weight children, with some kind of immaturity that may be related to the development of urolithiasis. A limitation of this report is that the number of patients involved is small, and both cases were extremely low birth weight children. Further investigations are warranted to clarify if infants with regular birth are less likely to develop urolithiasis. However, our experience suggests that combination therapy with ACTH and ZNS carries a high risk of developing urolithiasis, and this adverse effect can happen at an early date (urolithiasis was developed in a mere 10 days and 12 days, respectively, after starting the combination therapy). Regular urinalysis should be performed during therapy with these drugs, and if the presence of urolithiasis is suspected, CT scan or renal ultrasonography should be performed.

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