CASE REPORT

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Early diagnosis of neonatal-onset cyclic vomiting syndrome

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ABSTRACT

Cyclic vomiting syndrome (CVS) is characterized by recurrent episodes of severe vomiting with a completely asymptomatic interictal interval. Relatively few patients develop CVS in the neonatal period, and an early diagnosis is difficult. We experienced an infant who was diagnosed with neonatal-onset CVS in early infancy. An 8-day-old girl was admitted to our neonatal intensive care unit because of frequent vomiting beginning 12 h after birth and weight loss reaching 84.2% of her birth weight. Despite extensive examinations, no abnormalities to explain the vomiting were found. She continued to vomit, and a cyclical pattern with a vomiting phase lasting for three days followed by a non-vomiting phase lasting for about one to two weeks became obvious. Based on her clinical course, the family history of migraine and the effectiveness of Phenobarbital, she was diagnosed with CVS at three months old. Although CVS is a diagnosis of exclusion, a family history of migraine can aid its early diagnosis. If the illness is suspected in the neonatal period, diagnostic treatment with Phenobarbital may be considered. The case suggests the need to include CVS in the differential diagnosis of neonates with unexplained repetitive vomiting.

Keywords: migraine, phenobarbital, feeding disorder

Abbreviations:
CVS: cyclic vomiting syndrome
PB: phenobarbital
VPA: sodium valproate

INTRODUCTION

Cyclic vomiting syndrome (CVS) is characterized by recurrent episodes of severe vomiting with completely asymptomatic interictal intervals.[1] The mean age at the onset and diagnosis are 4.8 years old (6 days to 17 years old) and 9 years old, respectively.[2] Based on a previous report, the mean time span between first attack and the diagnosis of CVS was 2 ± 1.8 years (2

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months to 8 years).[2] The etiology of CVS is unknown, and its diagnosis is made after ruling out other diseases causing recurrent vomiting. While diagnosing CVS is very difficult,[1] most patients have only intermittent vomiting and generally lack life-threatening symptoms. The most important issue of CVS is the reduced quality of life.[3]

The most common cause of pathological vomiting in the neonatal period is gastro-esophageal reflux. Non-bilious vomiting during the neonatal period is generally followed up without treatment as long as the neonate shows no other symptoms and is in good general condition.[4] However, weight loss exceeding 10% of the current weight can indicate life-threatening conditions, including hypernatremic dehydration, which necessitate appropriate intervention.[5] Therefore, neonates with severe weight loss need an accurate diagnosis and treatment, even if functional non-bilious vomiting is suspected.

We herein report a patient who presented with non-bilious vomiting beginning immediately after birth and suffered severe weight loss, eventually being diagnosed with CVS in early infancy based on her clinical course, family history of migraine and effectiveness of Phenobarbital (PB).

CASE REPORT

A female infant weighing 3192 g at 39 weeks' gestation (appropriate-for-date) was delivered vaginally. The Apgar scores at 1 and 5 min were both 9. Her mother suffered from migraine and took analgesics daily. Oral mixed feeding was started 8 h after birth, and she began to present with non-bilious vomiting 12 h after birth. She continued to vomit frequently, and her weight decreased to 2689 g (84.2% of birth weight) at 8 days old, beyond the range of physiological weight loss. She was admitted to our neonatal intensive-care unit on the same day.

A physical examination was unremarkable except for weight loss and hypertension (95/49 mmHg) during vomiting. Blood tests, allergen lymphocyte stimulation test for non-IgE-mediated gastrointestinal food allergy, tests of inborn errors of metabolism, abdominal X-ray and ultrasonography, and upper and lower gastrointestinal fluoroscopy showed no abnormalities. With the continuation of vomiting after admission, she lost more weight and became lethargic. On suspicion of gastro-esophageal reflux and/or cow's milk allergy, TJ-43, an herbal remedy for vomiting, was administered, and breast milk and formula were switched to oral rehydration solution and subsequently to special formula for allergy. The results of an allergen lymphocyte stimulation test had not been obtained at that time.

However, she continued to vomit, and a cyclical pattern with a vomiting phase lasting for 3 days followed by a non-vomiting phase lasting for about one to two weeks became obvious (Figure). Based on the cyclical pattern of vomiting, normal electroencephalogram findings at 64 days old, and maternal history of migraine, which was noted after admission, we suspected CVS.

She showed a pale complexion, decreased vitality and a tendency toward somnolence during the vomiting period. The vomiting improved within two to three days, and the patient was very energetic during the non-vomiting phase. These symptoms were consistent with the criteria of Roma IV and NASPGHAN.[6] We tried to have her discharged during the non-vomiting phase, but she vomited every time discharge was scheduled. As the presence of hypertension suggested that the Sato variant type of CVS was most likely,[7] administration of sodium valproate (VPA) at 20 mg/kg/day was started at 64 days old. Thereafter, she showed no more vomiting and was able to drink more than 480 mL per day, the value initially suspected to trigger vomiting. As her ACTH, cortisol and ADH levels were normal (data not shown), the Sato variant type was excluded.

The patient was discharged at 81 days old after switching from special formula to ordinary formula. Immediately after returning home, she began to vomit again and was readmitted on

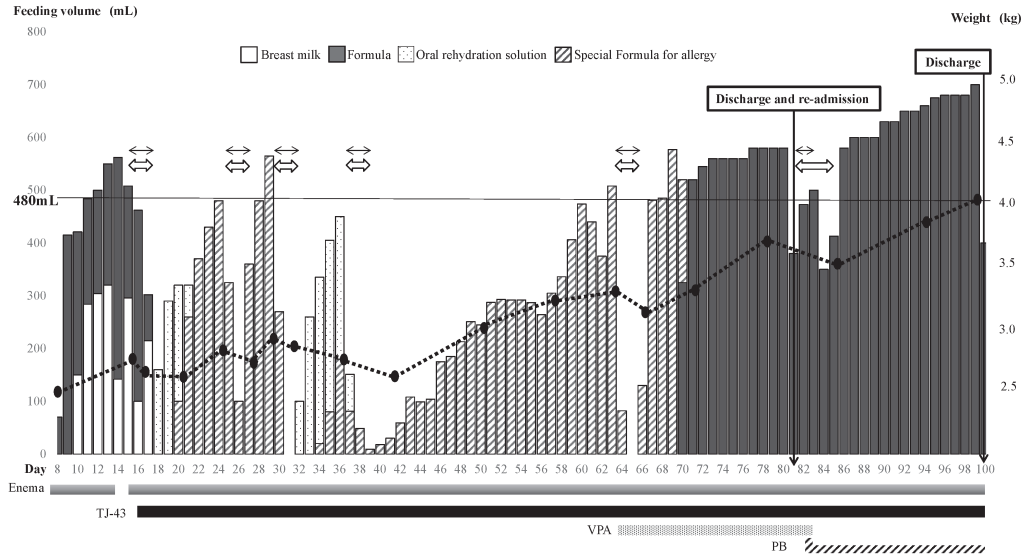

Fig. Clinical course of the patient
The black and white two-way arrows indicate vomiting and other symptoms including somnolence, pallor and poor vitality, respectively. Black dot-line graph indicates body weight.
VPA: sodium valproate
PB: phenobarbital
Enema: enema laxative

the same day. After switching from VPA to PB at 2 mg/kg/day, which is commonly used in neonates with CVS aside from the Sato variant type, she had no further vomiting episodes. However, PB at 2 mg/kg/day caused somnolence, so the dose was reduced to 1 mg/kg/day. Somnolence disappeared two days after dose reduction, and no vomiting attacks recurred. We finally diagnosed the patient with CVS.

Considering the paroxysmal nature of CVS, close observation was continued for 10 more days. She was discharged again at 100 days old after a total of 93 days admission in our neonatal intensive-care unit. At 1.5 years old, she is receiving PB at 1 mg/kg/day, and her growth and development are age-appropriate.

DISCUSSION

We encountered an infant with CVS who began to vomit 12 h after birth. This case indicates that CVS can arise even immediately after birth and suggests the need to include it in the differential diagnosis of neonates with unexplained repetitive vomiting.

Although the patient did not meet some items of the criteria of Roma IV and NASPGHAN[6] due to the early date of the diagnosis, CVS was suspected based on her clinical findings being otherwise consistent with such a diagnosis, such as a stereotypical onset and duration of vomiting and family history of migraine. She was treated initially with VPA and subsequently with PB. The diagnosis was confirmed based on the effectiveness of PB at three months old after ruling out various diseases presenting with neonatal vomiting other than CVS.

CVS is considered to be second only to gastro-esophageal reflux as a cause of recurrent

vomiting in children.[1] Although neonates and infants with recurrent non-bilious vomiting are often diagnosed with gastro-esophageal reflux, some may have CVS, and a substantial proportion of them may be undiagnosed and unable to receive proper treatment.[2] In general, the onset of CVS is in early childhood. Haghighat et al showed that CVS arose in the neonatal period in 5.5% of patients.[2] The earliest age of CVS onset has been reported to be 6 days old.[1] Interestingly, the onset in the present case was even earlier. The cyclical pattern of vomiting and family history of migraine led to the early diagnosis in this patient.

The incidence of migraine in families of CVS patients is 42%, and 44% of CVS patients eventually develop migraine themselves.[8] In addition, the usefulness of migraine medication as attack prophylaxis for CVS indicates that CVS is an analogous disease to migraine.[8] In the present case, VPA, a migraine prophylactic drug, was also able to suppress vomiting attack temporarily. In patients with vomiting with a family history of migraine, it is necessary to consider CVS as the differential diagnosis.

PB treatment for vomiting prophylaxis was successful in our patient. The NASPGHN consensus statement reported that cyproheptadine, propranolol, amitriptyline, phenobarbital, and pizotifen were associated with the highest response rates for prophylaxis.[9,10] Cyproheptadine is often used in children to treat CVS,[3] and its effectiveness has been reported to be 50%.[11] However, concerns about side effects in neonates remain. PB, by contrast, is a second-line drug for CVS prophylaxis.[9] Although there has been only 1 study reporting its effectiveness (78.6%),[12] this drug can be used safely even in preterm infants. In general, the PB dose for CVS prophylaxis is 2 mg/kg/day SID at bedtime.[9] In our case, this dose of PB caused somnolence. After the dose was reduced to 1 mg/kg/day, somnolence quickly disappeared, and no vomiting attacks recurred. If PB is ineffective, control of vomiting may be achieved in combination with VPA.[8] We did not use VPA in combination with PB in the present case because of concerns about hypersensitization. PB is easy to use and may be suitable for diagnostic treatment in neonates with recurrent vomiting of unknown etiology.

Separating babies from their parents in the neonatal unit can cause stress-related disorders in the parents, such as depression, post-traumatic stress disorder and anxiety, resulting in a negative impact on the parent-child relationship. It also adversely affects the baby's social and emotional development, behavior and cognitive functioning.[13] The early diagnosis of CVS is thus important for reducing the period of separation between mother and child and minimize the negative effects of such separation.

In conclusion, although neonatal-onset CVS is relatively rare, it should be included in the differential diagnosis of neonates with unexplained repetitive vomiting. If CVS is suspected based on the clinical course and family history, the diagnostic use of PB may be helpful.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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