

Topiramate can reduce the number of episodic attacks in cyclic vomiting syndrome : a case report

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Cyclic vomiting syndrome (CVS) is a paroxysmal, recurrent vomiting disorder of unknown pathophysiology and target organ. It has been hypothesized that CVS shares the same mechanism as migraine. We describe here a 5-year-old boy with CVS characterized by episodic vomiting attacks. These recurrent vomiting episodes began at 3 years of age, occurred every month and lasted for 5 days at a time. At the time of admission, no abnormal physical or neurological findings were observed and laboratory findings, including brain MRI and endoscopic examination, revealed nothing specific. The vomiting episodes were self-limited but recurrent and severely interrupted his daily life. When this patient was treated with topiramate, he showed a marked increase of symptom-free periods. (*Korean J Pediatr* 2007;50:386-389)

Key Words : Vomiting, Topiramate, Migraine, Child

Introduction

Cyclic vomiting syndrome (CVS) is an unusual cause of episodic emesis in children. It manifests as intermittent severe, recurrent, discrete, stereotypical episodes of vomiting, similar in time of onset and duration, with no symptoms during the intervening period. Most therapeutic interventions have proven unsuccessful in the prevention of emesis.

Following its initial description in 1881, CVS has been considered a variant of migraine^{1,2)}. Migraine headache, abdominal migraine, and CVS seem to be manifestations of the migraine diathesis, in that all are functional, self-limited episodic disorders separated by symptom-free intervals. The International Classification of Headache Disorders-2nd edition (ICHD-II) specifies 5 criteria for CVS: 1) the attacks must be episodic, stereotypical in individual patients, consisting of intense nausea and vomiting lasting 1 to 5 days; 2) vomiting during attacks must occur at least

5 times per hour for at least 1 hour; 3) there must be symptom-free periods between attacks; 4) the attacks cannot be attributed to another disorder; and 5) history and physical examination do not show signs of gastrointestinal disease³⁾.

The management of CVS remains empirical. Treatment is individualized and guided by recognition of the phase of illness at the time of treatment. During symptomatic periods, patients should be treated with intravenous hydration and other supportive care, including antiemetics and a proton pump inhibitor. During symptom-free intervals, patients should be treated prophylactically to ameliorate the factors that trigger these attacks. Due to the CVS-migraine relationship, the prophylactic agents used for CVS are those used in the prophylaxis of migraine headaches, including cyproheptadine, amitriptyline, and propranolol⁴⁻⁶⁾. Recent randomized controlled trials have shown that topiramate, a broad spectrum anticonvulsant, is effective in episodic migraine prevention⁷⁻¹⁰⁾. We describe here a 5-year-old child whose life had been severely disrupted by cyclic vomiting episodes and who showed great improvement after treatment with topiramate.

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Case Report

A 5-year-old boy with a history of recurrent episodes of vomiting and abdominal pain was admitted to the pediatric ward of Asan Medical Center in Seoul, Korea, for severe recurrent emesis. He had a history of pneumococcal meningitis at age 15 months, at which time he also showed right side hemiparesis and subdural effusions at both frontal convexities. This patient had gradually regained right side motor functions, and magnetic resonance imaging of the brain showed mild brain atrophy but no interval change. At the time of admission, he had a mild degree of language delay, but a general physical examination revealed no evidence of systemic illness or gastrointestinal disorders, except for moderate dehydration. Neurological findings were unremarkable, and all initial laboratory parameters were within the normal range. A detailed review of his family history did not reveal any relatives with migraine, epilepsy or other metabolic disorders.

The patient's recurrent vomiting episodes began at 3 years of age, initially occurring every 3 months and lasting for 5 days at a time. Recently, these episodes had occurred more frequently, every 20 to 25 days of symptom-free intervals. During these episodes, he could not ingest anything, even a sip of water, and experienced 20 to 30 vomiting episodes per day. However, he had no other associated symptoms, such as fever or headache. These episodes did not correlate with food intake, intercurrent illness, or psychosocial stress, and the patient was symptom-free between episodes.

An upper GI series revealed normal without gastroparesis, and esophagogastroduodenofiberoscopy showed mild chronic gastritis due to *Helicobacter pylori* infection and reflux esophagitis in the distal esophagus. The patient was initially treated with omeprazole, metoclopramide, and intravenous fluids, but his symptoms did not improve and may have been aggravated by the antiemetics, ondansetron and/or metoclopramide. On the sixth day in hospital, his symptoms disappeared and he recovered from the emesis attacks. The electroencephalogram showed anterior dominant slow wave discharges with occasional sharp waves, but there was no definite temporal relationship between the sharp wave discharges and his vomiting episodes.

We began treatment with 1.1 mg/kg/day topiramate, with the intention of titrating to 3.2 mg/kg/day topiramate over 2

weeks. Due to decreased sweating and fever, however, the patient ceased taking topiramate, without his doctor's knowledge, and he experienced another CVS attack the next day after 20 days of symptom-free period. We therefore re-started him on topiramate, titrating to a dose of 4.2 mg/kg/day. His symptom-free interval of cyclic vomiting dramatically increased, from 21.5 days to 75.3 days.

Discussion

CVS is a relatively rare and easily misdiagnosed disorder. Although its etiology and pathogenesis are still unclear, CVS is thought to be a variant of migraine, a hypothesis supported by the many similarities between the two disorders. Both CVS and migraine have similar temporal patterns, including rapid onset, duration of a few hours to days, and similar associated signs and symptoms¹¹. Moreover, the pathophysiological mechanisms contributing to CVS may be similar to those underlying migraine¹². In both diseases, the mechanisms of the attacks may involve dysfunction of brainstem structures^{12, 13}. Migraine and CVS may have genetic determinants and may be activated by various triggers. The majority of children with CVS have been subclassified as having migraine-associated CVS¹⁴⁻¹⁶. Since CVS and migraine share many distinctive features, such as transient paroxysmal attacks, precipitation by physiologic stresses, and apparent response to membrane stabilizing drugs, it is likely that a common pathogenetic mechanism is responsible for both disorders¹⁷.

Migraine and CVS are therefore regarded as chronic recurrent neurological disorders, in which an unknown mechanism gradually builds up an internal environment that favors the break-through of the characteristic attack. This attack, in turn, "unloads" the internal environment. If this hypothesis is correct, it may be feasible to prevent the next attack up to a few hours before that attack is due, provided that the organization of the internal terrain has not yet passed beyond a point of no return.

Migraine patients with high attack frequency, severe and disabling attacks, or poor response to acute treatment, as well as those who overuse acute medications, are candidates for prevention treatments. Topiramate has been shown to be effective in migraine prevention, and has been approved for this use in several countries^{7-9, 18}. Biologically, topiramate likely exerts its anti-migraine effect by suppressing neuronal excitation. Topiramate is thought to act on cellular mecha-

nisms of phosphorylation, to block voltage-dependent Na-channels and L- and N-calcium channels, to potentiate GABA activity, and to inhibit AMPA/ KA receptors¹⁹⁾. In addition, topiramate has been shown to inhibit cortical spreading depression in cat and rat models of migraine²⁰⁾.

In the case reported here, the condition of cyclic vomiting attacks met the consensus criteria for CVS^{3,11)}. This patient experienced recurrent severe discrete episodes of vomiting persisting for several days, as well as varying intervals of normal health between episodes, with no apparent cause of vomiting detected. Moreover, the symptoms were self-limited and stereotypical. The EEG findings of our patient were thought to be due to his remote brain injury. We cannot find no clinical correlation between his cyclic vomiting symptoms and the EEG findings.

Since CVS may be related to migraine, we treated this patient with the migraine preventive drug topiramate. He experienced marked improvement after starting treatment, and his symptoms were aggravated after temporary discontinuation of topiramate. Other than decreased sweating and mild fever, there have been no serious side effects. We cannot determine, however, if the cessation of vomiting episodes was caused by topiramate treatment or if it represents the natural course of his disease. Randomized controlled studies, in larger numbers of patients, are required to determine the effectiveness of topiramate in preventing CVS.

한 글 요약

Topiramate 투여로 호전된 주기성 구토증 1례

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주기성 구토증(cyclic vomiting syndrome, CVS)은 예측 불가능한 심한 구토가 특별한 원인 없이 시작되어 각 개인마다 일정한 임상 양상을 보이며 수 시간에서 수일간 지속되다가 저절로 호전되는 것을 반복하는 질환으로서, 그 임상 양상은 편두통과 많은 공통점을 보이며 그 병리생리학적 원인이 편두통과 유사한 것으로 추정되어지고 있다. 저자들은 만 3세 경 부터 시작된 발작적이고 반복적인 주기적 구토를 주소로 내원한 5세 남아에서 주기적 구토증을 진단하였으며, 이 환아에서 대규모의 임상 연구를 통해 단독 요법으로 편두통의 예방에 효능이 있음이 인정된 광범위 항경련제인 topiramate(TPM)를 투여하여 그 증상이 호전됨을 경험하고 이를 보고하는 바이다.

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