

Clonazepam Treatment of Pathologic Childhood Aerophagia with Psychological Stresses

The treatment of pathologic aerophagia has rarely been discussed in the literature. In this retrospective study, the authors investigated the effects of clonazepam on the management of pathologic childhood aerophagia (PCA) with psychological stresses (PS), but not with mental retardation. Data from 22 consecutive PCA patients with PS (aged 2 to 10 yr), who had been followed up for over 1 yr, were reviewed. On the basis of videolaryngoscopic views, the authors observed that the pathology of aerophagia was the result of reflex-induced swallowing with paroxysmal openings of the upper esophageal sphincter due to unknown factors and also observed that these reflex-induced openings were subsided after intravenous low dose benzodiazepine administration. Hence, clonazepam was administered to treat paroxysmal openings in these PCA patients with PS. Remission positivity was defined as symptom-free for a consecutive 1 month within 6 months of treatment. The results of treatment in 22 PCA patients with PS were analyzed. A remission positive state was documented in 14.3% of PCA patients managed by reassurance, and in 66.7% of PCA patients treated with clonazepam ($p=0.032$). Thus, clonazepam may produce positive results in PCA with PS. Future studies by randomized and placebo-controlled trials are needed to confirm the favorable effect of clonazepam in PCA.

Key Words : Aerophagia; Childhood; Clonazepam; Psychological Stress; Reassurance; Treatment

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INTRODUCTION

Pathologic aerophagia denotes the swallowing of excessive volumes of air, which causes various gastrointestinal symptoms, and is a clinical entity that simulates gastrointestinal motility disorders (1). Little information is available about the effectiveness of different therapies in pathologic childhood aerophagia (PCA) (2), and the management is largely reassurance for patients with psychological stresses (PS) (1-5). In patients with severe to profound mental retardation (MR) and massive bowel distention, the placement of a percutaneous endoscopic gastrostomy (PEG) catheter, which can be used to deflate, can prevent the complications of volvulus or perforation (6, 7).

Although PCA with PS is known as a benign disorder, 38.1% of patients have a symptom duration exceeding 12 months before diagnosis (8). Also, although reassurance and behavior therapies are potential treatments that can alleviate symptoms in aerophagia, only 50% of patients who had experienced short-term symptom improvement after behavior therapy maintained these improvements during a long-term follow up (8 months later) (2). Therefore, reassurance and behavior therapy may not be the ideal treatment for aerophagia.

In the PCA patients with PS, based on our videofluoroscopic investigations, we observed that the pathology of aerophagia seems to be due to reflex-induced swallowing due to unknown factors with paroxysmal openings of the upper esophageal sphincter, without the oro-pharyngeal swallowing movement sequences, followed by air swallows. We also observed in 5 PCA patients that these reflex-induced paroxysmal openings subsided after intravenous low dose benzodiazepine administration. Therefore, we agreed to try clonazepam, a benzodiazepine that is structurally related to chlordiazepoxide hydrochloride, to treat PCA with PS.

The treatment of pathologic aerophagia is rarely discussed in the literature, and few articles have been written about aerophagia in childhood (1, 2, 5-7). Here, we analyzed and evaluated the effects of clonazepam on the management of PCA with PS.

MATERIALS AND METHODS

Study population

We retrospectively analyzed the data from 22 consecutive

patients diagnosed with PCA patients with PS (9 female, 13 male; aged 2 to 10 yr), without severe to profound MR from March 1995 to July 2004. Patients were followed up for over 1 yr. They were recruited from the inpatient and outpatient units at the Dongsan Medical Center, Keimyung University School of Medicine. Informed consent was obtained from all parents of children treated with clonazepam, and all study procedures and medications were approved by the Keimyung University Institutional Review Board. Data were collected by reviewing medical charts, and followings were recorded and analyzed; age, underlying psychological stress factors, response and remission rate to treatments, and the effect of clonazepam. Clinical assessments of mental retardation were performed using the Denver Developmental Screening Test or the Social Maturity Scale. Psychological stress factors were identified using the Stressful Life-Change Event Scale (9). Parents provided a rating of stress in the patient's environment.

Fluoroscopic diagnosis of pathologic aerophagia

A diagnosis of pathologic aerophagia was made if the observed symptomatic abdominal distention was due to the swallowing of air, as confirmed by videofluoroscopy, and if it was not attributable to any gastrointestinal disease, i.e., mechanical intestinal obstruction, chronic intestinal pseudo-obstruction, bacterial overgrowth, Hirschsprung's disease, or malabsorption. These pathologies were considered initially and then ruled out by clinical findings and progress, and according to bowel transit times using sitz marker, gastrofiberscopic mucosal biopsy, or other tests as needed. A diagnosis of pathologic aerophagia, based on the videofluoroscopic observations, was defined as the presence of reflex-induced swallowing due to unknown factors with paroxysmal openings of the upper esophageal sphincter, followed by air swallows, but without oro-pharyngeal swallowing movement sequences (8).

Assignment of the two management groups

In PCA patients with PS, parents were advised to choose between two management protocols (reassurance or clonazepam treatment) for PCA. Accordingly, patients were assigned into two management groups; a reassurance group (7 patients) and a clonazepam group (15 patients). We performed an open-labeled trial with clonazepam only in PCA patients with parental consent and compared the effect of clonazepam in this group with findings in the reassurance group.

Trial of clonazepam and reassurance

Benzodiazepine is a commonly used medication for myoclonus-like paroxysmal movements (10). In the present study, we injected low dose of diazepam (1-3 mg) intravenously in 5 PCA patients with PS under videofluoroscopic observation.

Paroxysmal openings subsided a few minutes after injection, but sedation was not induced. These findings were recorded on a videotape and thoroughly analyzed by a consensus among the authors. Hence, we administered oral clonazepam (Rivotril[®], Korea Roche) to PCA patients with given parental consent, but unfortunately this was not placebo-controlled. At a body weight of less than 30 kg, the initial dosage was 0.025 mg/kg/day in two divided doses. Doses were incremented by 0.025 mg/kg every 3 to 5 days as needed; the usual maintenance dosage was 0.1 mg/kg. For body weights exceeding 30 kg, the initial and maintenance dosages were 1.5 mg daily in two divided doses. No patient had a clonazepam-contraindicating disease or condition, such as, liver disease, renal impairment, or narrow-angle glaucoma. Blood concentrations were monitored monthly, and parents were informed of possible side effects and were instructed to carefully observe patients. Clonazepam was prescribed for 1 month and discontinued if the response was negative. However, if the response was positive, it was continued for an additional 4 months or to symptom-free for a consecutive 1 month. Clonazepam treatment was discontinued by tapering over an additional 1 month.

Reassurance of patients and parents was performed on every visit at an out-patient clinic by a pediatric gastroenterologist, who addressed the clinical characteristics and natural course of the pathologic aerophagia and periodically assessed clinical symptoms and disease progress, and by a pediatric psychiatrist, who rated mental retardation, identified psychological stress, and provided psychiatric support to patients and patients' family members in terms of coping with stress.

Definition of response and remission

To evaluate treatment effects, we defined response positive as being symptom-free for a consecutive 1 week within 1 month of treatment and remission positive as being symptom-free for a consecutive 1 month within 6 months of treatment. Interviews were conducted to parents at out-patient clinic at intervals of 1 week during the first month of treatment, and thereafter at 2-week intervals. Each parent observed and recorded; 1) abdominal distention during the late evening, 2) symptoms (abdominal discomfort, increased flatus, and increased flatus while sleeping, and visible or audible air swallowing sound) during the late evening, and 3) bowel sounds as determined by ear on the patient's abdomen during the late evening. In case of increased abdominal distention, a positive clinical symptom and increased bowel sound (8), we defined that the symptom-free state had not been achieved during that day.

Statistical analysis

Fisher's exact test was used for the statistical analysis. Statistical significance was accepted at $p < 0.05$. Data were presented as mean \pm SD.

RESULTS

Age distribution and psychological stress factors

The average age of the 22 PCA patients was 5.9 ± 2.6 yr (range, 2-10 yr). There were no significant differences between the two treatment groups in terms of age, sex, or symptom duration. PCA was precipitated by the following psychological stress factor; school or preschool entrance (31.8%), birth of siblings (22.7%), a working mother (13.6%), divorce of parents (9.1%), being scolded (4.5%), a mother's psychosis (4.5%), hospital admission (4.5%), toilet training (4.5%), and trouble with a sibling (4.5%).

Response and remission by treatments

None of the patients treated with clonazepam showed any side effect. The treatments administered to the 22 PCA with PS patients were reassurance ($n=7$) and clonazepam ($n=15$). None of PCA patients managed by reassurance achieved a response positive state, but 40.0% of PCA patients treated with clonazepam did ($p=0.067$). A remission positive state occurred in 14.3% of PCA patients managed by reassurance and in 66.7% of PCA patients treated with clonazepam ($p=0.032$) (Table 1). No recurrence of aerophagia occurred in the reassurance or clonazepam group that achieved a remission positive state during the 6 months of follow-up after remission.

DISCUSSION

A review of the literature (1-8) shows that the main underlying associations of pathologic aerophagia are severe to profound mental retardation and identified psychological stresses. In PCA patients with identified PS, the psychological stress factors are problems that are frequently encountered during child development. Moreover, patients are otherwise healthy children, but are highly sensitive individuals (4). Environmental factors such as stress and attention seeking have been suggested to be the causes of aerophagia (3, 4).

Table 1. The results of response and remission according to the treatments of children with pathologic childhood aerophagia with identified psychological stress factor

	Response*		Remission†	
	Positive	Negative	Positive	Negative
Reassurance ($n=7$) (%)	0 (0.0)	7 (100.0)	1 (14.3)	6 (85.7)
Clonazepam ($n=15$) (%)	6 (40.0)	9 (60.0)	10 (66.7)	5 (33.3)

* $p=0.067$, † $p=0.032$.

*Defined as being symptom-free for a consecutive 1 week within 1 month of treatment. †Defined as being symptom-free for a consecutive 1 month within 6 months of treatment.

When the movement of a bolus from the oral cavity to the pharyngeal space triggers the swallowing reflex or response, the subsequent physiological events leading to the esophageal phase are mainly controlled by the anatomophysiological network, designated the 'central pattern generator' of swallowing. When this is triggered, sequential muscle activity begins in an orderly fashion from the facial- and trigeminal-innervated muscles to the cricopharyngeus sphincter muscle and striated esophageal muscles (11). Innervation of the cricopharyngeus muscle has been the subject of much debate. The consensus view is that the cricopharyngeus muscle has a dual innervation by the pharyngeal plexus of the vagus nerve (tenth cranial nerve) and the recurrent laryngeal nerve (12). Our observations indicate the possibility of that pathologic aerophagia as a reflex-induced movement of the cricopharyngeus sphincter may be induced by any pathology of the neurological swallowing sequence. Unfortunately, we had not performed submental muscle electromyography or cricopharyngeal sphincter electromyography to evaluate abnormalities of 'central pattern generator'. The neurophysiology of swallowing in patients with pathologic aerophagia must be further evaluated.

We suspect that pathologic aerophagia may stem from psychogenic movement disorders, which means that non-epileptic physiological myoclonus-like movement may be induced by anxiety (9, 13). Therefore, we undertook to trial clonazepam for the treatment of PCA. In patients with identified PS factors, no response was achieved in any of the reassurance group patients, but was achieved in 40.0% of the clonazepam group patients. This result was of borderline significance, but it suggests that reassurance itself may not induce a response. Remission occurred in 14.3% of patients managed by reassurance, and in 66.7% of patients treated with clonazepam. These observations show, although management by reassurance itself may improve pathologic aerophagia in patients with identified psychological stresses, that clonazepam treatment is significantly more effective at inducing remission of pathologic aerophagia than reassurance. However, clonazepam may affect centrally to relieve the patient from stress and also may exert a placebo effect. These effects may induce a positive response or remission to some degree in patients with PCA. The background of psychophysiology and of neurological disorders in patients with pathologic aerophagia must be further evaluated, and in addition, the relationship between the causative role of psychological stresses and reflex-induced swallowing with paroxysmal upper esophageal sphincter openings should be further evaluated.

In conclusion, pathologic aerophagia appears to be due to the reflex-induced swallowing from unknown factors. Moreover, this study shows that in PCA patients with PS, clonazepam may achieve positive results. Unfortunately, a randomized trial could not be performed due to the low incidence of PCA. To the best of our knowledge, this is the first trial of clonazepam in PCA. Future study based on a random-

mized, placebo-controlled trial is needed to confirm the favorable effect of clonazepam in PCA.

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