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Original Article

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Clonazepam Treatment of Pathologic Aerophagia in Children with Mental Retardation

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Purpose: Pathologic aerophagia (PA) may lead to bowel perforation or volvulus in mentally retarded patients. The authors investigated the effects of clonazepam on the management of PA in children with severe to profound mental retardation (MR).

Methods: This study was undertaken as a retrospective case analysis of 21 PA patients with MR who were followed for over 12 months and diagnosed as having PA. Patients were assigned to two management groups, that is, to a clonazepam randomized open-labeled, treatment group or a reassurance group. The following were recorded and analyzed; age, response, remission rate to clonazepam treatment, and the side effect of clonazepam. It was defined positive response (response+) as being symptom-free for a whole week within 1 month of commencing treatment and remission(+) as being symptom-free for a whole month within 6 months of treatment.

Results: The average age of the 21 PA children with MR was 10 years and 13 patients were female. Symptom duration before diagnosis of PA was 7 months. Clinical features of the clonazepam-trial group (n=11) and the reassurance group (n=10) were non-significantly different. Response(+) was achieved by 2 patients (18.2%) in the clonazepam-trial group and by no patient in the reassurance group. Remission(+) was achieved by 6 patients (54.5%) in the clonazepam-trial group and by one patient (10%) in the reassurance group (p=0.040).

Conclusion: When PA children with MR with severe bowel distention are considered for surgical treatment to prevent acute abdomen, a trial of clonazepam could be recommended.

Key Words: Aerophagy, Child, Intellectual disability, Clonazepam

INTRODUCTION

Pathologic aerophagia (PA) is condition involving the swallowing sufficient air to cause gastrointestinal symptoms [1]. PA may be observed in 8.8% of the institutionalized mentally retarded population [2]. However, the cause of PA in these patients has not been determined.

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In patients with severe to profound mental retardation (MR), aerophagia may cause massive distention of the bowel and lead to perforation or volvulus [3-6]. In general, surgical emergencies in mentally retarded patients are difficult to diagnose because of problems associated with obtaining a reliable medical history and physical examination.

To prevent massive and persistent bowel distention that could potentially result in surgical emergencies, the placement of a percutaneous endoscopic gastrostomy (PEG) [7] has been suggested. Fukuzawa et al. [8] recently suggested a method of surgical bowel reconstruction (i.e., esophagogastric separation and abdominal esophagostomy via jejunal interposition) to evacuate swallowed air and prevent severe bowel distention.

Hwang et al. [1,9] observed by laryngoscopy and fluoroscopy that PA is the result of involuntary paroxysmal cricopharyngeal sphincter openings of the esophagus, like myoclonus, and that these are followed by air swallowing. In addition, PA has also been reported in Tourette's syndrome [10] and in a vocal tic disorder [11], which supports the observation by Hwang et al. [1,9].

Benzodiazepine is a commonly used medication for myoclonus. Hwang et al. [9] also observed in a trial of low dose diazepam in PA patients that treatment might induce subsidence of involuntary openings of upper esophageal sphincter, and suggested that clonazepam may be effective in some patients with PA with psychological stress factors [9].

This study was conducted as a randomized, open-labeled, non-placebo-controlled, study to evaluate the effect of clonazepam on PA in children with severe to profound MR.

MATERIALS AND METHODS

The data of 21 PA children with MR who were followed for over 12 months and were diagnosed to have PA between September 2004 and February 2011 were analyzed. Patients were recruited from the inpatient and outpatient units at the Department of Pediatrics, Dongsan Medical Center, Keimyung University School of Medicine. The 21 patients were assigned to two management groups; a clonazepam-trial group and a reassurance group. The study was performed using a randomized open-labeled, non-placebo-controlled design. Clonazepam was administered only after obtaining informed consent from parents. The results obtained were compared with those of a reassurance group. The following were recorded and analyzed; age, response and remission rates to clonazepam treatment, and the side effects of clonazepam. MR was clinically assessed using the Denver developmental screening test or the social maturity scale. The study was approved by the institutional review board of Keimyung University (DSMC 2014-08-042).

PA was diagnosed using previously reported diagnostic guidelines [1]. Clonazepam treatment and reassurance management were performed as described previously [9]. We administered oral clonazepam (Rivotril; Korea Roche, Seoul, Korea) to PA patients with given parental consent. 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. Blood concentrations were monitored monthly, and parents were informed of possible side effects and were instructed to carefully observe patients. 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 PA and periodically assessed clinical symptoms and disease progress; and by a pediatric psychiatrist, who rated MR, identified psychological stress, and provided psychiatric support to patients and patients' family members in terms of coping with stress.

To evaluate the effects of treatment, we defined positive response (response+) as being symptom-free for a whole week within 1 month of treatment and remission(+) as being symptom-free for a whole month within 6 months of treatment.

Table 1. The Results of Response and Remission according to the Clonazepam Treatment of Pathologic Childhood Aerophagia Patients with Mental Retardation

Group	Response*		Remission†	
	Positive	Negative	Positive	Negative
Clonazepam (n=11)	2 (18.2)	9 (81.8)	6 (54.5)	5 (45.4)
Reassurance (n=10)	0 (0.0)	10 (100.0)	1 (10.0)	9 (90.0)

Values are presented as number (%).
*Defined as being symptom-free for a whole week within 1 month of treatment, p=0.262. †Defined as being symptom-free for a whole month within 6 months of treatment, p=0.040.

Interview with parents was performed on out-patient clinic basis at fortnightly intervals during the first month of treatment and thereafter at 4 week intervals. Abdominal girth was checked daily during early mornings and late evenings before sleep and recorded by parents. Before sleep, parents listened for and recorded bowel sounds by placing an ear on the patient's abdomen; on the day when abdominal girth was checked for more than 10 cm increased compared to the one of not-distended condition and also when bowel sound was increased, that particular day was defined as non-symptom free.

Statistical analysis was conducted using SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL, USA). All values are expressed as mean±standard deviation. Fisher's exact test or the χ^2 test were used for the statistical analysis, and statistical significance was accepted for p-values <0.05.

RESULTS

The average age of the 21 study subjects was 10 years (range, 4-19 years) and 13 patients were female. Symptom duration before diagnosis was 7 months (range, 2-16 months). Clinical features were not different between the clonazepam-trial group and the reassurance group; mean ages were 10 (4-18) years in clonazepam-trial group and 10 (5-19) years in the reassurance group; gender ratios (female : male) were 7 : 4 in clonazepam-trial group and 6 : 4 in reassurance group; and mean symptom durations before final diagnosis were 7 (2-16) months and 6 (2-14) months, respectively.

The results of the two treatments are summarized in Table 1. Response(+) was observed in 2 patients (18.2%) in the clonazepam-trial group and in no patient in the reassurance group. Remission(+) was observed in 6 patients (54.5%) in the clonazepam-trial group and in one patient (10%) in the reassurance group (p=0.040).

No clonazepam-related side effect was observed.

DISCUSSION

This study shows that in PA children with MR, clonazepam may achieve positive results in about 50% of patients treated. When patients with massive and persistent bowel distention are being considered for PEG [7] or surgical bowel reconstruction [8], a trial with clonazepam may produce satisfactory results and avoid the need for these invasive procedures. To the best of our knowledge, this is the first trial of clonazepam in PA children with MR.

The main underlying associations of PA are psychological stresses and severe to profound MR [1]. In most PA patients with identified psychological stress factors, pathologic air swallowing may resolve spontaneously, but in PA patients with MR, resolving of air swallowing is not as frequent [1,4,8]. Habitual air swallowing in MR patients may be impossible to stop, and although rare, it may result in bowel perforation or volvulus [3-6]. The cause and mechanism of air swallowing in PA has not been clearly determined. It has been suggested that air swallowing in MR patients is a means of self-destruction or of dealing with boredom [3,12].

Compared to our previous study of clonazepam effectiveness in PA children with psychological stresses [9], the present study of colonazepam treatment in PA patients with MR was less effective in response rate (40.0% vs. 18.2%) and in remission rate (66.7% vs. 54.5%). Moreover, almost all cases of surgical conditions associated with PA were observed in mentally retarded patients [3-8]. These observations mean that PA with MR may be more difficult to manage and may progress to more intractable in its course than PA only with psychological stresses.

Interestingly, the increase in vocal tics has been associated with an increase in psychological stresses and the development of PA [10,11]. Hwang et al. [1,9] used fluoroscopy in combination with laryngoscopy to observe oro-pharyngo-esophageal movements associated with voluntary or involuntary air swallowing in PA patients, and revealed that involuntary air swallowing results from the presence of reflex-induced swallowing due to paroxysmal repetitive openings of the upper esophageal sphincter, followed by air swallowing, but without oropharyngeal swallowing movement sequences. In line with this observation, esophageal impedance monitoring in PA patients [13,14] recently showed that despite a normal swallowing frequency, a high incidence of air swallowing is characteristic of PA. Hwang et al. [1,9] suggested that PA may originate from psychogenic movement disorders, which indicates non-epileptic physiological myoclonus-like movement may be anxiety induced. Relations between the causative roles of psychological stresses or severe and profound MR and air swallowing by vocal tic-like movements [10,11] or reflex-induced swallowing with paroxysmal upper esophageal sphincter openings [1,9] required further evaluation.

Blondeau et al. [15] recently reported that baclofen, a γ-aminobutyric acid (GABA) agonist, may improve symptoms of rumination, supragastric belching, and PA. Baclofen has been shown to increase basal lower esophageal sphincter pressure, and it has been hypothesized in PA that baclofen decreases swallowing frequency, and thus, air ingestion, and improves symptoms. Unfortunately in this previous study, the authors only observed one patient with predominant PA.

Baclofen is a primarily muscle relaxant used to treat spastic movement disorders, and is beneficial in Tourette syndrome [16], a chronic neuropsychiatric disorder associated with the presence of involuntary motor and vocal tics. Interestingly, clonazepam (a benzodiazepine) also acts on GABA receptors and decreases symptoms in patients with typical tics [17-20]. Accordingly, we suggest that the effects of baclofen and clonazepam effects in PA might be due to their ameliorative effects on vocal tic-like movements [10,11] or on involuntary paroxysmal upper esophageal sphincter openings [1,9], which in turn suggests PA is a clinical type of neuropsychiatric disorder.

GABAergic neurons are essential components of frontal-subcortical circuits, the proposed pathophysiologic site in Tourette syndrome or tics [21]. Further assessment is needed to determine whether these brain circuits are also associated with pathologic air swallowing.

The present study shows that clonazepam treatment is significantly more effective at inducing PA remission than reassurance. We suggest the possibility that clonazepam acts centrally to relieve stress. A placebo-controlled trial is mandatory to ascertain more clearly the effect of clonazepam in PA.

We conclude that clonazepam treatment can achieve positive results in PA children with MR. When such patients with severe bowel distention are being considered for PEG or bowel reconstruction to prevent surgical emergencies, we would recommend a trial with clonazepam before these invasive procedures are adopted. Finally, we suggest that further studies be conducted to establish the backgrounds of psychophysiology and of neurological disorders in patients with PA.

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