Gastroesophageal reflux in neurologically impaired children : What are the risk factors?

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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Background/Aims: Neurologically impaired patients (NIP) frequently suffer from gastrointestinal tract problems such as gastroesophageal reflux disease (GERD). In this study, we aimed to define the risk factors for GERD in neurologically impaired children. Methods: From May 2006 to March 2014, 101 neurologically impaired children who received 24 hr esophageal pH monitoring in Severance children's hospital were enrolled. The results of esophageal pH monitoring and the clinical characteristics of the patients were analyzed. Results: Reflux index was higher in the abnormal EEG group than in the normal EEG group (p = 0.027). Mitochondrial disease was associated with a higher reflux index than epileptic disorders or cerebral palsy (p = 0.009) Patient gender, feeding method, scoliosis, tracheostomy, and baclofen use did not lead to statistical differences in reflux index. Age of onset of neurological impairment was inversely correlated with DeMeester score and reflux index. Age at the time of examination, duration of the disease, and number of antiepileptic drugs did not correlate with GER severity. Conclusions: Early-onset neurologic impairment, abnormal EEG, and mitochondrial disease are identified as risk factors for severe GERD.

Key words: gastroesophageal reflux, esophageal pH monitoring, child

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I. INTRODUCTION

As the central nervous system controls the enteric nervous system, neurologically impaired patients (NIP) frequently suffer from gastrointestinal tract dysfunction[1]. Guidice et al.[2] reported that 92% of children with cerebral palsy had clinically significant gastrointestinal symptoms: gastroesophageal reflux, 77%; swallowing disorders, 60%; chronic pulmonary aspiration, 41%; and chronic constipation, 74%. Decreased lower esophageal sphincter tone, delayed gastric emptying, impaired esophageal motility, poor posture, recurrent seizures, scoliosis, and various medications are thought to contribute to gastroesophageal reflux disease (GERD) in neurologically impaired children[3]. Respiratory symptoms, which are frequent in NIP, are also thought to aggravate GERD [4]. Despite its high incidence, GERD in neurologically impaired children is difficult to recognize as the symptoms of GER are nonspecific and many patients cannot precisely express their symptoms. Therefore, diagnosis of GERD in NIP is often delayed until severe esophagitis or fatal aspiration pneumonia occurs[5]. As GER is closely related with aspiration pneumonia or food refusal, this can be a large obstacle to appropriate nutritional support of NIP, which can result in a poor clinical prognosis. This is why physicians should pay attention to GER in NIP. Early suspicion and evaluation can prevent

severe complications of GERD in NIP and can lead to better clinical outcomes. In this study, we analyze the degree of gastroesophageal reflux according to patient characteristics and define the risk factors for GERD in neurologically impaired children.

II. MATERIALS AND METHODS

1. Study Population and Data Collection

Data from pediatric patients who received 24 hr esophageal pH monitoring in Severance children's hospital from May 2006 to March 2014 were collected. Of those cases, neurologically impaired children were selected for the study. The reasons for performing 24 hr esophageal pH monitoring varied, but most patients had symptoms of gastroeophageal reflux such as recurrent aspiration pneumonia, grunting after meals, frequent regurgitation, and unexplained food refusal or unexplained irritability, or tonic posture. Patients who received upper gastrointestinal operations such as Nissen fundoplication or whose medical records were incomplete were excluded from this study. Finally, 101 patients (median age, 23.4 months) were enrolled. The results of esophageal pH monitoring and the clinical characteristics of the patients were analyzed. Patient selection and data collection were performed by retrospectively reviewing medical records. The protocol of this study was approved by the Institutional Review Board of Severance Hospital.

2. 24 hr esophageal pH monitoring

To allow for an accurate diagnosis, histamine 2 receptor antagonist and proton pump inhibitor medications were discontinued at least 3 days and 7 days before examination, respectively. Prokinetic drugs were also discontinued more than 3 days. A pH monitoring catheter probe was inserted through the nose to the distal esophagus. The tip of the pH electrode was placed on the third vertebral body above the diaphragm, as confirmed by fluoroscopy. Reflux index (%), the percentage of the time during the investigation in which pH < 4, was used for analysis. DeMeester score, which reflects the number of acid refluxes, number

of long acid refluxes, duration of the longest acid reflux, and fraction of time that the pH was below 4.00, were also used for the comparison.

3. Statistical Analysis

Reflux index was compared between groups according to diagnosis, feeding type (oral feeding, nasogastric tube feeding, or gastrostomy feeding), scoliosis status, ventriculo-peritoneal shunt status, tracheostomy status, electroencephalography (EEG) results, and baclofen use. These clinical characteristics are compared between GERD group and non GERD group as well. GERD was defined according to reflux index. For infant and children, less than 11.7% and 5.4% were considered physiologic reflux respectively. Correlations of reflux index and DeMeester score to disease onset age, age at examination, duration of disease, and number of antiepileptic drugs were analyzed as well. The Mann-Whitney test, Kruskal–Wallis test, chi-square test, and Spearman correlation test were used for the analysis. All statistical analyses were performed using SPSS software (version 18.0, SPSS Inc., Chicago, IL). A p value < 0.05 was considered statistically significant.

III. RESULTS

Patients were divided according to their clinical characteristics. Distributions and descriptive statistics are given in Table 1.

Table 1. Patient Characteristics

A

Category	N (%)
Gender	
Male	59 (58.4)
Female	42 (41.6)
EEG	
Normal	9 (8.9)
Abnormal	92 (91.1)
Baclofen	
With baclofen	19 (18.8)
Without baclofen	82 (81.2)
Tracheostomy	
With tracheostomy	9 (8.9)
Without tracheostomy	92 (91.1)
V-P shunt	
With V-P shunt	5 (5.0)
Without V-P shunt	96 (95.0)
Scoliosis	
With scoliosis	36 (35.5)
Without scoliosis	65 (64.4)

Feeding route	
Oral	45 (44.6)
Nasogastric tube	48 (47.5)
Gastrostomy	8 (7.9)
Main Diagnosis	
Epilepsy	67 (66.3)
Mitochondrial disease	19 (18.8)
Cerebral palsy	8 (7.9)
Others	7 (6.9)
Brain MRI	
Normal	25 (24.7)
Abnormal	76 (75.2)
Total	101 (100)

V-P shunt, ventriculo-peritoneal shunt

B

Category	Median (IQR)
Disease onset age (month)	3 (0-6)
Examination age (month)	23.4 (10.5-44.1)
Duration of disease (month)	15.4 (7.35-30.75)
Number of AED	3 (2-4)

IQR, interquartile range; AED, antiepileptic drug

All patients were under the age of 18. Causes of neurologic impairment were heterogeneous and included perinatal asphyxia, genetic abnormality, cerebral hemorrhage or infarction, hypoxic brain damage, brain tumor, and infections of

the central nervous system. Substantial numbers of patients had developed neurologic impairment without a definite cause. The main diagnoses of the patients were variable as well, such as Lenox-Gastaut syndrome, infantile spasm, cerebral palsy, mitochondrial disease, Dravet syndrome, and so on. As many patients had complex and combined diagnosis, patients with confirmed mitochondrial disease were categorized to mitochondrial disease group priorly, and patients who have epilepsy but not diagnosed with mitochondrial disease were categorized to epilepsy group. Patients with cerebral palsy were categorized to cerebral palsy group only when diagnosed with neither mitochondrial disease nor epilepsy. When we compared reflux index according to disease category, the mitochondrial disease group (n = 19) had a higher reflex index than did the other epilepsy group (n = 67) or the cerebral palsy group (n = 8) (p = 0.009). The median reflux index values were 14.4, 3.9, and 3.5, respectively. Patient gender, feeding method, scoliosis, tracheostomy, and baclofen use did not lead to statistically significant differences in reflux index. Reflux index was significantly higher in the abnormal EEG group than in the normal EEG group (p = 0.027) (Fig. 1).

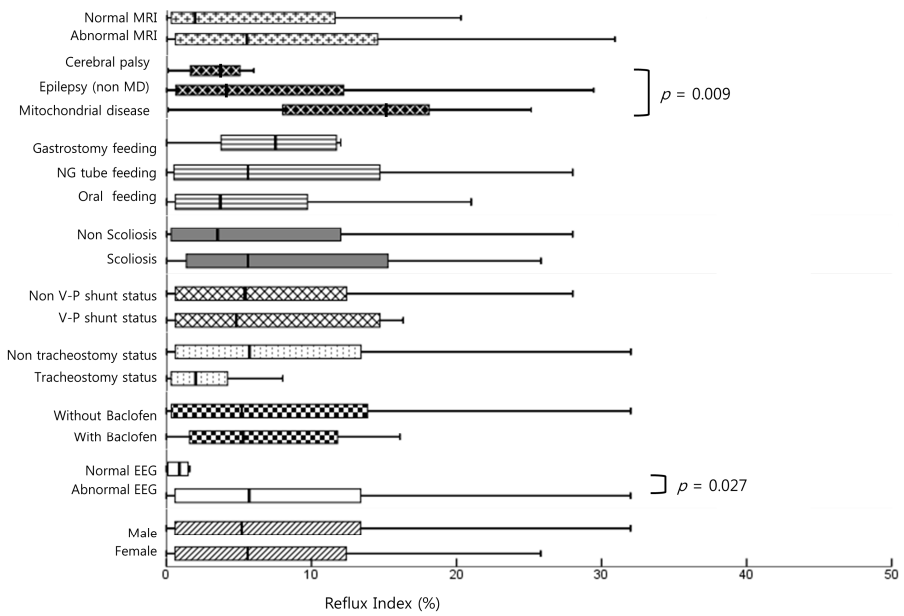

Fig. 1. Box and whisker plot of reflux index showing the distribution of reflux index according to clinical condition. The box represents the interquartile range, and the line in the box shows the median value. Differences with a p value of < 0.05 are marked.

Clinical characteristics between GERD group and non GERD group did not have significant difference (Table2.)

Table 2. Spearman correlation coefficients of gastro-esophageal reflux index and DeMeester score with continuous variables

	DeMeester score		Reflux index	
	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value
Disease onset Age	-0.389	< 0.001*	-0.371	< 0.001*
Examination Age	-0.31	0.760	-0.050	0.621
Disease duration	0.180	0.071	0.159	0.113
Number of AED	0.083	0.409	0.122	0.224

The age at examination, duration of the disease, and number of antiepileptic drugs did not correlate with reflux index or DeMeester score. However, age of onset of neurological impairment was inversely correlated with DeMeester score (correlation coefficient -0.389; $p < 0.001$). Reflux index (%) and disease onset age also demonstrated a similar tendency (correlation coefficient -0.371; $p < 0.001$), which means that early onset of neurologic impairment can aggravate GER (Table 3).

Table 3. Comparisons of clinical characteristics between GERD and non-GERD group

	GERD (n = 35)	non GERD (n = 66)	p-value
Male (%)	18/35(51.4)	41/66(62.1)	0.204
EEG abnormality (%)	34/35(97.1)	58/66(87.9)	0.114
Baclofen use (%)	6/35(17.1)	13/66(19.7)	0.489
Tracheostomy (%)	1/35 (2.9)	8/66 (4.5)	0.114
V-P shunt (%)	2/35(5.7)	3/66(36.4)	0.569
Scoliosis (%)	12/35 (34.3)	24/66 (36.4)	0.507
MRI abnormality (%)	8/35 (22.9)	58/66 (87.9)	0.422

When we analyzed reflux index according to disease onset age, patients who had disease onset before 12months showed higher reflux index (8.77 ± 9.33) than patient who had disease onset after 12months of age (4.16 ± 6.66) and the result was statistically significant (p = 0.025).

IV. DISCUSSION

GER refers to retrograde passage of gastric contents to the esophagus, pharynx, or oral cavity. GERs can be normal physiological events which occur frequently even in healthy individuals[6]. However, severe GER can cause troublesome symptoms or complications and can impair health-related quality of life[7]. This condition is called GERD. GERD is much more prevalent in NIP than in the normal population, and can be a significant obstacle to ensuring adequate nutrition. In clinical practice, neurologically impaired children are often malnourished and malnutrition and GER can negatively impact one another[8,9]. Therefore, both conditions should be monitored and managed attentively. Furthermore, due to a lack of effective communication, GERD is often diagnosed belatedly. GER is also closely related to respiratory problems. Recurrent pulmonary infections can be caused that give rise to poor prognoses[10]. Thus, GERD can decrease a patient's quality of life both directly and indirectly. If GER can be predicted in NIP, appropriate evaluation and management measures can be taken which will lead to better long-term outcomes.

Although GER is a relatively common problem in both normal infants and NIP, the mechanisms of GER are not fully understood. Transient relaxation of the lower esophageal sphincter (LES) has been reported to be a main mechanism of GER in children[11,12]. On the other hand, in NIP, absence of LES tone is thought to be the main mechanism rather than transient relaxation of the LES[13]. Delayed gastric emptying and decreased antroduodenal motor function have also been suggested as mechanisms of GER in NIP[14,15]. As the mechanisms of GER in NIP are complicated and poorly understood, it is difficult to predict and prevent GERD in such patients. This study was designed to identify the risk factors for the GER in neurologically impaired children.

In this study, early-onset neurological impairment was related to more severe

GER. This finding may be because early-onset neurological diseases tend to be related to congenital neurologic anomalies or genetic mutations which bring about major neurologic sequelae, and accordingly, severe systemic complications. In a previous study, 67% of otherwise healthy infants were found to have GER at 4 months of age[16]. This is due to frequent feeding, short esophagus, the wide angle between the esophagus and stomach, and the amount of time infants spend in the supine position rather than in an upright position[17]. This physiologic GER was alleviated in the course of normal growth, development, and transition to solid food. Only 5% of otherwise healthy children have GER at 12 months of age[16]. In early-onset NIP, such normal developmental progress can be halted and GER may persist throughout life. In this study, patients who developed neurological impairment before 12 months of age revealed to have higher reflux index than other patients (8.77 ± 9.33 vs. 4.16 ± 6.66). Therefore, additional attention to GERD and aspiration is necessary especially for patients with infantile-onset neurologic impairment. Although we also hypothesized that a long duration of morbidity might affect the severity of GER, the two were not significantly associated. Disease duration does not seem to be a significant factor for progression of GER in NIP.

The clinical manifestations of neurological diseases are different according to the diagnosis. Therefore, we compared the severity of GER amongst patient with different categories of disease. As the causes and diagnoses of neurologic impairment were heterogeneous, we categorized them as mitochondrial disease, epileptic disorders other than mitochondrial disease, cerebral palsy, and others. Patients with mitochondrial disease showed a higher reflux index than did those with other diseases. Mitochondrial disease is a multi-systemic disorder that is frequently associated gastrointestinal and hepatic manifestations[18]. Bhardwaj et al.[19] demonstrated that children with mitochondrial disease had frequent gastrointestinal symptoms, such as abdominal pain, GER, and constipation, which are thought to be related to delayed gastric emptying and small bowel

transit time, and which respond poorly to medications. This result suggests that NIP with mitochondrial disease is at additional risk for GER. Not only neurologic impairment but also mitochondrial disease itself may contribute to this result. However, additional randomized controlled studies are required to fully elucidate this matter.

In a previous study, somewhat different characteristics were seen between nasogastric tube fed and orally fed children, and orally fed NIP were at an increased risk for aspiration[1]. Feeding route and physical characteristics of food may influence the upper gastrointestinal motility and gastric emptying. However, in the present study, statistical differences were not observed between the gastrostomy, nasogastric tube, and orally fed groups. As patients in the three groups tended to have different clinical conditions, confounding factors may have affected the results.

To compare objective conditions, the patients with ventriculo-peritoneal shunts or tracheostomy or scoliosis were analyzed with the patients who did not have the conditions. As a result, such conditions did not statistically affect reflux activity. In terms of electroencephalography, the normal EEG group had a lower reflux index than did the abnormal EEG group. This means that abnormal EEG can be considered a risk factor for GERD in NIP. However, this does not mean that seizure activity aggravates GERD directly, as the number of antiepileptic drugs, which is an indicator of intractable seizures, is not correlated with reflux activity. Rather, abnormal brain function itself most likely affected reflux activity.

As many patients with neurological problems suffer from tonic posture, baclofen is sometimes used as a muscle relaxant. Because it is as GABA type B receptor agonist, baclofen is known to decrease postprandial acid reflux by reducing transient lower esophageal sphincter relaxation[20,21]. Kawai et al. reported that administration of baclofen reduced the frequency of emesis and

acid reflux in neurologically impaired children[22]. Although we attempted to investigate the anti-reflux effect of baclofen in this study, no significant differences existed between the baclofen-treated group and the group not taking baclofen. This result may be negatively affected by spasticity itself, the reason for baclofen treatment.

This study has several limitations. First, the study population was heterogeneous. Patients with several different types of neurological impairments were included, and their clinical conditions were variable. Second, the reasons for performing 24 hr esophageal pH monitoring were diverse. Some patients had severe recurrent aspiration pneumonia, whereas others had mild irritability. The decision to perform the test depended individual physicians, which may have introduced a selection bias. Furthermore, the study design was retrospective.

V. CONCLUSION

As several complex clinical factors may influence GER, it is difficult to predict the degree of GER just by using objective clinical factors in severely ill, neurologically impaired children. However, as the results of this study show, early onset neurologic impairment, mitochondrial disease, and abnormal EEG can be important risk factors for severe GER. Accordingly, early suspicion and proper evaluations of GER are needed for those patients.

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ABSTRACT(IN KOREAN)

신경학적 장애가 있는 소아에서 위식도역류의 위험인자

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김 승

배경/목적: 신경학적으로 장애가 있는 환자들은 위식도역류병과 같은 위장관의 증상을 동반하는 경우가 매우 흔하다. 본 연구에서는 신경학적 장애가 있는 소아환자들을 대상으로 하여 위식도역류병의 위험인자를 규명하고자 하였다. 방법: 세브란스 어린이 병원에서 2006년 5월부터 2014년 3월까지 24시간 식도 pH검사를 진행한 환자 중 신경학적 장애가 있는 101명을 대상으로 하였으며, 24시간 식도 pH 검사 결과와 환자의 임상적 특성을 분석하였다. 결과: Reflux index는 비정상 뇌파를 보인 군에서 정상뇌파를 보인 군보다 높은 소견을 보였다(p = 0.027). 환자의 진단명으로 구분하였을 때 미토콘드리아 질환이 뇌전증 또는 뇌성마비 군보다 높은 reflux index와 연관이 있었다(p = 0.009). 환자의 성별, 식이방법, 척추측만증, 기관절개여부, 뇌실-복강단락여부, baclofen사용여부와 reflux index와는 상관관계를 보이지 않았다. 신경학적 질환의 발생나이와 DeMeester score, reflux index와는 역의 상관관계를 보이고 있었으나, 검사당시의 나이, 신경학적 질환의 이환기간, 환자가 복용중인 항경련제의 갯수는 위식도역류의 심한 정도와 상관성을 보이지 않았다. 결론: 이른 나이(12개월 이전)에 발생한 신경학적 장애, 비정상적인 뇌파소견, 미토콘드리아질환은 심한 위식도역류질환의 위험인자로 생각된다.

핵심되는 말 : 위식도역류, 24시간 식도 pH검사, 소아