Prevalence and Risk Factors for Gastroesophageal Reflux in Symptomatic Very Preterm Neonates

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Research

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Abstract

Background Because of immature development, preterm infants are prone to respiratory and digestive symptoms of dyspnea, vomiting, and aspiration pneumonia. These symptoms are often observed in infants with gastroesophageal reflux (GER). However, the relationship between GER and these symptoms remain unclear.

Methods A cohort of 61 preterm infants born at 32 weeks of gestation or earlier with respiratory or digestive symptoms were retrospectively reviewed. All the preterm infants underwent 24-hour pH-multichannel intraluminal impedance monitoring. Clinical data were analyzed using logistic regression analyses.

Results Among the 61 symptomatic preterm infants, 34 were positive for pathologic GER with a prevalence of 55.7%. The GER associated symptoms included apnea (42.6%), cyanosis (19.7%), vomiting (14.8%), pneumonia (9.8%), and poor weight gain (13.1%). These respiratory and digestive symptoms were more frequent in infants with pathologic GER than in those without. ($p<0.05$) The risk factors for GER included severe BPD (odds ratio [OR], 6.890; 95% confidence interval [CI], 1.125-42.209). Probiotics and delayed full oral feeds reduced the risk of GER (odds ratio [OR], 0.642; 95% confidence interval [CI], 0.457-0.901, $p<0.05$; OR, 0.234, 95% CI, 0.069-0.794, $p<0.05$).

Conclusions The prevalence of GER is high in the symptomatic preterm infants. GER aggravates the respiratory and digestive symptoms holding that not all the symptoms are GER associated. Probiotics and delayed full oral feeds can decrease the prevalence of GER.

Background

Gastroesophageal reflux (GER) is common in infants because of physiological factors such as immaturity of the lower esophageal sphincter (LES), supine positioning, and frequent feeding. It was initially thought that approximately 70–85% of infants with regurgitation required no intervention within the first 2 months of life (1). However, infants with GER may have symptoms such as vomiting, poor weight gain, dyspnea, decreased oxygen saturation, and aspiration pneumonia. The presence of these conditions has been defined as gastroesophageal reflux disease (GERD) (2). Improvements in medical technology used for infant care have allowed for the survival of an increasing number of preterm infants and infants with very low birth weight. More than 80% preterm infants may experience the clinical symptoms of GERD. However, diagnosing GER is difficult; therefore, the incidence of GER and its effects on infants are controversial.

Traditionally, 24-hour pH monitoring has been the gold standard technique for diagnosing GER. However, it cannot diagnose nonacidic episodes with pH 4, which occur in infants because continuous feedings dilute the gastric acid. Mitchell et al. (3) reported that the stomach has a pH 4 during only approximately 24.5% of total time; with the range from 0.6–69.1%. Because nonacid reflux is the most common type of reflux for infants, the multichannel intraluminal impedance (MII) technique, which overcomes the

disadvantages of traditional 24-hour pH monitoring, has become a valid method used to diagnose GERD in preterm infants (4). With this method, the diagnostic accuracy has been significantly improved. This study aimed to investigate symptomatic preterm infants using gastric and esophageal 24-hour pH-MII monitoring to determine the prevalence, clinical features and risk factors of GER in very preterm infants.

Materials And Methods

This retrospective cohort study involved infants born at 32 weeks of gestation or earlier at a regional tertiary care neonatal intensive care unit (NICU) between November 2016 and November 2019. The inclusion criteria were gestational age (GA) ≤ 32 weeks and clinical symptoms indicative of GER (including apnea, cyanosis, recurrent vomiting, aspiration pneumonia, poor weight gain) according to the criteria of the North American Society for Pediatric Gastroenterology and Nutrition (5). Apnea was defined as breathing pauses lasting for more than 20 s, or for more than 10 s together with bradycardia or oxygen desaturation (6). Cyanosis was judged by blood oxygen desaturation below 80%. The exclusion criteria included digestive system abnormalities, congenital heart disease, neurological disorders, inherited metabolic disease, cow milk allergy, and death (7).

A total of 61 infants with clinical symptoms consistent with GERD whose parents agreed to gastric and esophageal 24-hour pH-MII monitoring were enrolled in this study. No surgeries were performed for GER. Written informed consent was obtained from the parents of all included patients. The study was approved by the Ethics Committee of the Shengjing Hospital of China Medical University (protocol no. 2017PS084J).

Equipment for gastric and esophageal 24-hour pH-MII monitoring

A pH monitor (Digitrapper™ PH-Z; Medtronic Inc., Minneapolis, MN, USA) was connected with a probe containing one pH channel and six impedance channels (Z1-Z6; Kanglian, Beijing, China). The probe was a single silicone probe and the catheter consisted of monocrystalline antimony electrodes. The probes were calibrated before each study. Data were evaluated using the manufacturer's software (Reflux Reader v6.1 Software Updates) after each study.

All infants underwent ambulatory 24-h pH-MII measurements performed with gastric and esophageal probes connected to the device when they could ingest milk via breastfeeding or bottle. During the study, all infants were breathed spontaneously, received an intermittent bottle, were not administered orogastric feeds, and were not administered antireflux or antacid medications, inhaled medications, or diuretics. Infants were kept in the supine position during monitoring. The neonatal pH probe was orally inserted in the esophagus. The esophageal probe position was verified by chest radiography performed 2 to 3 cm proximal to the LES. According to the Strobel formula, the probe length (cm) was $0.87 \times (0.252 \times \text{height} + 5)$ (4). The gastric probe was placed on the fundus of the stomach. Both the esophageal pH and gastric pH were monitored. Each tracing was manually reviewed and validated by the same operator. Patients were monitored for 24 hours. Nurses documented the feeding times and symptoms during the observation period.

Definition of reflux episodes

GER was diagnosed based on the proximal pH channel. Reflux index (RI), which is the percentage of the total recording time with an esophageal pH < 4, was used to categorize pathological GER. Acid reflux was defined as abnormal when the RI was ≥ 7%, irrespective of the impedance value (8). The esophageal liquid caused a decrease in impedance that persisted as long as the bolus was present between the two electrodes and returned to baseline when the liquid was cleared (9). In the present study, weakly acidic reflux was defined as pH between 4 and 7 and impedance values that decreased to > 20% of the baseline value. The diasal pH channel showed that the pH was < 4 in the stomach during more than 50% of 1 day. Nonacidic GER was diagnosed when the RI was < 7%, the impedance values decreased, and the intragastric pH was < 4 during less than 50% of total 24 h (10). For each pH-MII examination, the following variables-number of reflux episodes, duration of the longest reflux event, reflux events lasting > 5 minutes, symptom index (SI), symptom sensitivity index (SSI), symptom-associated probability (SAP)-were also evaluated.

Statistical analysis

Continuous data were analyzed using the independent samples t test, and the results are presented as means ± standard deviations. Noncontinuous data were assessed using the chi-square test and Fisher's exact test. Univariate variables with $p < 0.1$ were introduced in a binary logistic regression analysis using the Forward Wald method. Adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated for all variables. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

Demographics

Sixty-one preterm infants (33 male and 28 female infants) with a median GA of 30 ± 1.28 weeks (range, 26^{+5} weeks to 32 weeks) and a mean birth weight (BW) of 1409 ± 362 g were reviewed. They received complete oral feeds at a median PMA of 35 ± 2.1 weeks. All patients remained clinically stable and accepted the monitoring well. No one received medication for GER during hospitalization.

GER prevalence in symptomatic preterm infants

Among the 61 infants with symptoms, 34(16 female and 18 male infants, 56%) were GER-positive and 27 (44%) were GER-negative. Eighteen (53%) cases of acid reflux and 16 (47%) cases of other reflux (including weakly acidic and nonacidic reflux) occurred in GER-positive infants. Table 1 presents the GA and birth weights. There were no difference between GER positive and GER negative group classified by GA and BW ($p = 0.886$, 0.538 respectively). A similar result was found between acid reflux group and other reflux group classified by GA and BW ($p = 0.797$, 0.052 respectively).

Table 1
Cohort characteristics of patients (n = 61)

Factors	Grade	GER positive, n (%)			GER negative
		acid reflux	other reflux	total	
GA	< 28w	1(5.6%)	2(12.5%)	3(8.8%)	2(7.4%)
	28-30w	7(38.9%)	6(37.5%)	13(38.2%)	13(48.2%)
	30-32w	10(55.6%)	8(50%)	18(53%)	12(44.4%)
BW	< 1000 g	1(5.6%)	5(31.3%)	6(17.6%)	3(11.1%)
	1000–1500 g	6(33.3%)	7(43.7%)	13(38.2%)	14(51.9%)
	> 1500 g	11(61.1%)	4(25%)	15(44.2%)	10(37%)
GA: gestational age, BW: birth weight					

Among the 34 infants GER-positive for GER, 53% (18/34) had acid reflux, 26.5% (9/34) had weakly acidic reflux, and 20.6% (7/34) had nonacidic reflux. Acid reflux-positive preterm infants (10 male and 8 female infants) born at 30.12 ± 0.97 weeks of gestation (range, 28–31^{+6} weeks of gestation) had an average weight of 1530.83 ± 266.35 g (range, 973–1900 g). Eight male and eight female GER-positive infants with weak acidic or nonacidic reflux were born at 29.78 ± 1.53 weeks of gestation (range, 26^{+5}-32 weeks of gestation) and had an average weight of 1336.63 ± 482.16 g (range, 695–2355 g).

Relationship between GER and the symptoms

Among the 61 infants, 26 (42.6%) had apnea, 12 (19.7%) had cyanosis, 9 (14.8%) had vomiting, 6 (9.8%) had pneumonia, and 8 (13.1%) had poor weight gain. By SSI and SAP analysis, the GER associated symptoms included apnea (52.9%), cyanosis (17.6%), vomiting (8.8%), pneumonia (5.9%), and poor weight gain (14.7%). There was no difference in the aforementioned reflux-related symptoms for those in the GER-negative and GER-positive groups according to the chi-square test (Table 2). But these symptoms were more frequent in the GER-positive group than those in the GER-negative group, indicating that GER might aggravate these symptoms ($p < 0.05$).

Table 2
Relationship between GER and the symptoms

Symptoms	GER negative, n (%)	GER positive, n (%)	t/χ^2	*P*
apnea	8(29.6)	18(52.9)	3.344	0.067
cyanosis	6(22.2)	6(17.6)	0.199	0.655
vomiting	6(22.2)	3(8.8)	2.148	0.143
pneumonia	4(14.8)	2(5.9)	1.354	0.245
poor weight gain	3(11.1)	5(14.7)	0.171	0.680

Risk factors for GER in the symptomatic preterm infants

As shown in Table 3, there were no significant differences in the general conditions and clinical characteristics, including sex, GA, BW, Apgar score at 1 minute, PMA at the time of the study, duration of partial parenteral nutrition, caffeine administration, duration of mechanical ventilation, length of hospital stay, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and nosocomial infection, for the GER-negative and GER-positive groups according to the independent samples t test (all $p > 0.05$). The durations of noninvasive auxiliary ventilation were statistically significant for the GER-negative and GER-positive groups (14.67 ± 9.1 vs 8.71 ± 7.9, $p < 0.01$). Infants of GER-positive group had earlier full oral feeds compared to those of GER-negative group (35.18 ± 2.16 vs 36.26 ± 1.45, $p < 0.01$). More probiotics was used in GER-positive group than in GER-negative group ($p < 0.05$). Though there was no difference of BPD between the two groups, severe BPD was more often in GER-positive group than that in GER-negative group ($p < 0.05$).

Table 3
Risk factors of GER negative group and GER positive group

Clinical features	GER negative (27)	GER positive (34)	t/χ^2	*P*
female, n (%)	12(44.4)	16(47.1)	0.041	0.839
GA (weeks)	29.96 ± 1.41	29.96 ± 1.26	-0.001	0.999
BW (g)	1371 ± 327	1439 ± 390	-0.733	0.467
Apgar score at 1 min	7.59 ± 2.08	7.88 ± 1.75	-0.59	0.557
PMA at full oral feeds (weeks)	36.26 ± 1.45	35.18 ± 2.16	2.851	0.006
PMA at study (weeks)	35.71 ± 1.86	35.21 ± 1.59	0.939	0.352
durations of PPN (days)	27.37 ± 13.67	22.68 ± 15.50	1.237	0.221
caffeine administration (days)	17.89 ± 10.5	12.35 ± 11.04	1.988	0.051
duration of mechanical ventilation (days)	7.41 ± 10.5	3.76 ± 5.5	1.742	0.087
duration of noninvasive auxiliary ventilation (days)	14.67 ± 9.1	8.71 ± 7.9	2.740	0.008
length of hospital stay (days)	52.44 ± 16.81	48.11 ± 22.55	0.83	0.410
probiotics, n (%)	17(63.0)	12(35.3)	4.620	0.032
BPD, n (%)	8(29.6)	13(38.2)	0.494	0.482
severe BPD, n (%)	2(7.4)	10(29.4)	4.611	0.032
NEC, n (%)	3(11.1)	0		0.081*
nosocomial infection, n (%)	6(22.2)	7(20.6)	0.024	0.877
*Calculated by Fisher's Exact Test				
GA: gestational age, BW: birth weight, PMA: postmenstrual age, PPN: partial parenteral nutrition, BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis.				

A binary logistic regression analysis using caffeine administration, duration of mechanical ventilation, duration of noninvasive auxiliary ventilation, probiotics, severe BPD, and NEC (univariate $p < 0.1$) revealed that delayed full oral feeds and probiotics could decrease the GER risk (odds ratio [OR], 0.642; 95% confidence interval [CI], 0.457–0.901, $p = 0.01$; OR, 0.234, 95% CI, 0.069–0.794, $p = 0.02$). Severe BPD increased the GER risk (OR, 6.890; 95% CI, 1.125–42.209; $p = 0.037$) (Table 4).

Table 4
Logistic regression analysis of risk factors for GER

Risk Factors	B	Sig	Exp (B)	Exp (B) 95% CI	
				Lower	Upper
PMA at full oral feeds	− .443	0.010	0.642	0.457	0.901
probiotics	-1.453	0.020	0.234	0.069	0.794
severe BPD	1.930	0.037	6.890	1.125	42.209

Discussion

As a physiologic phenomenon, GER is especially common in preterm infants. A 3-year retrospective study of 18,567 premature infants at 33 medical centers in North America found that the morbidity of GERD was as high as 10.3% for premature infants and that the lower the weight, the higher the morbidity (11). The diagnosis of GERD is difficult when based only on nonspecific clinical symptoms. In this study, we found that the prevalence of GER for preterm infants was 56%, and there was significant clinical suspicion of reflux. Jadcherla et al. found that the prevalence of GER was 54%; symptoms associated with GER were observed in 30 symptomatic infants with acid reflux (48.5%) and nonacid reflux (51.5%) (12). These results were similar to those of our study. Funderburk et al. reported that the prevalence of GER detected by pH-MII monitoring was only 10% for symptomatic term and preterm infants (13), and that irritability, bradycardia, and desaturation were common signs and symptoms, which was not in accordance with our results. These differences may have been caused by the different subjects and clinical symptoms. In this study, we also found that most cases existed in infants with a GA of 30–32 weeks and birth weight more than 1500 g, which is in accordance with the prevalence in North America (11). The reason was not clear and was thought to be due to a prematurity-associated decrease in acid production.

Infants born before 32 weeks of gestation are prone to apnea because of immature respiratory center. While apnea triggered by feeding may be likely GER related. Hypoxemia post-feeding may also be due to incoordination between milking and breathing, immature laryngeal chemoreflex, or diaphragmatic fatigue. In Australia and the United States, almost half of all board-certified neonatologists believe that apnea is caused by GERD and are likely to recommend acid suppressors (14, 15). Cresi et al. found the associations of GER and cardiorespiratory events such as apnea existed in 12% of infants and most of them were caused by non-acidic reflux events (6). But some studies speculated that there is no relationship between apnea and GER in preterm infants (16, 17). Nobile et al. studied 47 infants and found only 11% infants with GER was associated with symptoms of apnea or cyanosis. And weaklyacid refluxes were more often (18). Although it is commonly thought that GER could cause apnea, some studies of humans have concluded that apnea precedes a reflux episode and that reflux does not cause apnea (19, 20). In this respective study, we could not analysis the causal association between asphyxia and apnea. In our study, as a common phenomenon for both GER-negative and GER-positive infants,

apnea affected nearly half of them (52.9%). It has been reported that the prone position is helpful for alleviating obstructive apnea (21). This mechanism may have decreased the occurrence of GER. Some studies indicated that weakly acidic reflux events, but not acid reflux events, are more prevalent in premature infants (22). Shin et al. studied 23 infants suspected of having GERD based on pH-MII monitoring and found that the main symptom was apnea, with acid flux accounting for only 40.8% of all episodes (23); our results are similar to theirs.

Caffeine was often used to prevent BPD or apnea in very premature infants (24). And it was interesting that we also found infants with GER had less caffeine usage though there were no difference between GER positive group and GER negative group. The reason may be that caffeine delayed the gastric emptying time of preterm infants. It was verified according to ultrasound assessments (25).

Low birth weight preterm infants who are unable to suck oral feeds are required to be fed via an intragastric tube for varying lengths of time. There were no difference of effect on RI between small-bore and large-bore nasogastric (NG) tubes (26). It was also reported that there was no significant difference on acid exposure no matter with or without the NG tube. But preterm infants without an NG tube had significantly more reflux events regardless of GA and birth weight (27). In the study, no association was found between earlier oral feeding and acid reflux. But it was found that delayed oral feeding could decrease the risk of GER. The reason may be that the infants could tolerate and accommodate feedings better with the progress of postnatal corrected age. So we recommented not to remove the gastric tube prematurely.

Traditionally, probiotics was thought beneficial to prevent gastrointestinal disorders such as acute gastroenteritis, antibiotic-associated diarrhoea, or necrotising enterocolitis (28). However, no broad consensus exists to recommend the use of probiotics in the prevention of GER. A Systematic Review mentioned that totally 11 of 14 studies (79%) reported positive efficacy of probiotics on reflux symptoms in adults (29). A prospective, multicenter, double-masked, placebo-controlled randomized clinical trial found that Lactobacillus reuteri DSM (L. reuteri) 17938 for 3 months reduced the onset of functional gastrointestinal disorders including GER in term neonates (30). Using real-time ultrasound observing, L. reuteri DSM 17938 was confirmed efficient in improving reflux by accelerating gastric emptying (31). In our study, the probiotics chosen was L. reuteri. We found that L. reuteri effectively prevent the occurrence of GER. However, the role of L. reuteri still needs to be studied in large sample, multi-center clinical study.

The potential interrelationship of GER events is relevant not only to probiotics but also to severe BPD. In our study, there was no relationship between GER and BPD or necrotizing enterocolitis or nosocomial infection. But severe BPD poses potential risk factor for GER. Until now, the relationship between GER and BPD is controversial. GERD reportedly causes a significant increase in both BPD and NEC, thus leading to increased costs because of the resultant prolonged hospital stay (11). In a prospective observational cohort study that enrolled a total of 46 preterm infants born before 32 weeks of gestation and suspected of having GERD, infants with BPD had increased pH-only events and a corresponding symptom sensitivity index, probably because of the lower milk intake, impaired esophageal motility, or a peculiar

autonomic nervous system response pattern. There was no difference in morbidity due to GER or clinical characteristics of the two groups, irrespective of the presence of BPD (32).

The limitations of the study include the limited number of cases and the retrospective observational study design; therefore, further prospective studies are needed to confirm our results. Finally, GERD in preterm infants is often overdiagnosed by the present method of 24 h pH monitoring. Despite these shortcomings, the benefits of the treatment of GER in symptomatic preterm infants warrants further technical refinement and wide application.

Conclusions

The prevalence of GER is high in the symptomatic preterm infants. GER aggravates the respiratory and digestive symptoms holding that not all the symptoms are GER associated. Probiotics and delayed full oral feeds can decrease the prevalence of GER.

Abbreviations

GER = Gastroesophageal reflux, BPD = Bronchopulmonary Dysplasia, Odds ratio=OR, Confidence interval=CI, Lower esophageal sphincter =LES, Gastroesophageal reflux disease=GERD, GA = Gestational Age, PMA = postmenstrual age, pH-MII = pH-multichannel intraluminal impedance, Reflux index=RI, SI=Symptom Index, SSI = Symptom Sensitivity Index, symptom-associated probability=SAP, necrotizing enterocolitis=NEC.

Declarations

Ethics approval and consent to participate:

The Ethics Committee of China Medical University (2017PS084J) approved the protocol and written informed consent was obtained from all parents.

Consent for publication:

Not applicable.

Availability of data and material:

The datasets generated for this study are available on request to the corresponding author.

Author Contributions:

Yu Hu collected and analyzed the clinical data. JianHua Fu designed the study. ShuCheng Zhang drafted and revised the manuscript. All authors read and approved the final manuscript.

Competing interests:

The authors have no financial relationships relevant to this article to disclose. The authors have no conflicts of interest relevant to this article to disclose.

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