BMC Pediatrics

RESEARCH

Open Access

24 h combined esophageal multichannel intraluminal impedance and pH monitoring in children with chronic cough

Yi Gan[1], Xiaoqin Zhou[1], Zhaoxuan Huang[1], Shan Gao[1], Guirong Wang[1], Li Gu[1], Di Zhang[1], Lingzhi Yan[1], Shanshan Shang[1], Junhua Shu[1*] and Danna Tu[1*]

Abstract

Background Chronic cough in children is closely related to gastroesophageal reflux (GER). However, this association has not been adequately studied due to a lack of diagnostic tools. Combined esophageal multichannel intraluminal impedance and pH (MII-pH) monitoring is considered the most accurate method for evaluating the association between symptoms and reflux, but data on its use in children with chronic cough are still lacking. We aimed to assess the association between chronic cough and GER in children through MII-pH monitoring.

Methods Children with chronic cough (> 4 weeks) who were suspected gastroesophageal reflux disease(GERD) were selected to undergo 24 h MII-pH monitoring at our hospital. Patients were divided into groups according to their age, body position, reflux index (RI) or total reflux events, and the differences between the groups were analyzed. Then the significance and value of 24 h pH and impedance monitoring in chronic cough and the relationship between chronic cough and reflux were discussed.

Results Overall, 426 patients were included. The median age was 12 months (interquartile range: 6–39.5 months), 129 (30.3%) patients had RI > 7% detected by pH-metry, and 290 (68.1%) patients had positive diagnosis based on the impedance data. GER predominantly occurred in the upright position and mostly involved weakly acidic reflux and mixed gas–liquid reflux. There were 14.1% of children in non-acid GER group were SAP positive showing no difference in acid GER group 13.2% ($P = 0.88$), whereas patients with SAP > 95% in MII positive group (47[16.2%]) is higher than in MII negative group ($P < 0.05$).

Conclusion Twenty four hour MII-pH monitoring is safe, well tolerated in children, but also has a higher detection rate of gastroesophageal reflux. It can find identify weakly acidic reflux, weakly alkaline reflux and reflux events with different physical properties, which can explain the relationship between GER and chronic cough more comprehensively. It provides new approach for exploring the etiology, diagnosis and treatment of children with chronic cough.

Keywords Pediatrics, Children, Chronic cough, Gastroesophageal reflux

Introduction

For children aged ≤ 14 years, chronic cough is defined as cough that persists for > 4 weeks [1]. Previous epidemiological studies have suggested an association between GERD and chronic cough [2]. Often, children with GERD do not have typical symptoms of regurgitation,

*Correspondence:
Junhua Shu
sfysjh2011@163.com
Danna Tu
tdn_tutu@163.com
Full list of author information is available at the end of the article

heartburn, vomiting, failure to thrive, abdominal pain, and dysphagia.

GERD has not been commonly identified as the cause of pediatric cough due to the lack of accurate diagnostic tools for pediatric GERD [3]. The various objective methods for diagnosing GERD include endoscopy, pH-metry (also known as pH monitoring), and MII-pH monitoring [4]. pH monitoring was developed in the 1990s, and for a long time, it was regarded as the best technique for measuring reflux [5]. However, this technique cannot detect all gastroesophageal reflux events, particularly when little or no acid is present in the refluxate. MII-pH monitoring has been recommended as a valuable alternative for detecting and evaluating gastroesophageal reflux, as it can effectively analyze the characteristics and components of refluxates, identify liquid and gas reflux, and differentiate between acid and non-acid reflux [6]. However, due to the high cost of MII-pH monitoring and its poor compliance in children, it has not been widely used in pediatrics.

Therefore, in the present study, we aimed to assess the association between chronic cough and gastroesophageal reflux detected through 24 h MII-pH monitoring. To the best of our knowledge, this was the first study in which 24 h MII-pH monitoring was used in a large sample of pediatric patients with chronic cough to study the relationship between chronic cough and gastroesophageal reflux in children. In addition, the characteristics of 24 h MII-pH for chronic cough in children are described.

Methods

The 24 h-MII-pH-monitoring results of 428 children with chronic cough (cough persisting for > 4 weeks) who underwent MII-pH monitoring for 24 h at Hubei Maternal and Child Health Hospital between 2017 and 2020 were analyzed in this study. Children were included if they were aged 0–14 years and had not received any acid-suppressive drugs or drugs that affect gastric motility in the two weeks preceding their examination. Two patients were excluded due to intolerance and short monitoring duration. This study was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. The parents or guardians of all participants provided written informed consent to take part in the present study.

The MII-pH monitoring device allowed for the simultaneous recording of esophageal multichannel intraluminal impedance and pH (Ohmega; Laborie, Enschede, the Netherlands). Ideally, the pH probe tip should be positioned in the lower esophagus at 87% of the total esophageal length [7]. For infants, we applied the Strobel formula (0.252*body length [cm] + 5) to localize the LES [8]. For children, we combined pH gradients to localize the LES, then confirmed by radiography. The patients and their guardians were encouraged to maintain normal activities, sleep schedules, meal types, and mealtimes. Before the study, the guardians and older children were instructed to press the "event" buttons on the device in case of specific symptoms. They were also asked to complete a written diary reporting any symptoms, meal and sleeping times, and position changes (supine/upright). The chemical properties of reflux were detected by pH probe, which were categorized into acidic (pH < 4.0), weakly acidic (pH 4.0–7.0) and weakly alkaline reflux (pH > 7.0), with the latter two defined as non-acidic reflux [9]. The physical properties of reflux were distinguished by MII monitoring(Liquid reflux: from the impedance channel of the last end, there are at least two continuous impedance channels in the retrograde, and the impedance value decreases by > 50%.;Pure gas reflux: the impedance value increases rapidly > 5000 in at least two continuous impedance channels.;Mixed reflux: Gas reflux occurs immediately before or simultaneously with liquid reflux).

Symptom-association probability (SAP) correlated symptoms to refluxes. The entire recording of MII-pH was divided into consecutive 2-min time windows and assessed for the presence of reflux in each time window. In combination with symptom time and the number of all the symptoms recorded in the journals, each 2-min period of the recording was classified into reflux alone (R + S −), reflux followed by symptom (R + S +), only symptom but no reflux (R − S +), and neither reflux nor symptom (R − S −). When a symptom occurred in the 2-min span after a reflux event, it was considered as "associated to reflux" [9]. A value greater than 95% was considered statistically significant. Patients were divided into an acid GER and non-acid GER group based on reflux index (RI); RI indicates the percentage of the entire esophageal record having a pH < 4.0. Patients with RI > 7% were included in the acid GER group, and those with RI ≤ 7% were included in the non-acid GER group [10, 11]. A positive diagnosis based on the impedance data defined as total reflux events > 100 in patients aged < 1 year or > 70 in patients aged ≥ 1 years [12].Variables with values that were not normally distributed are presented as the median (interquartile range [IQR]). Median values were compared using the Mann-Whitney U test. Pearson correlation was used for associations between sequential parameters. All statistical analyses were performed using SPSS software (Version26.0;SPSS,Inc.,Chicago, IL,USA). P-values < 0.05 were considered statistically significant.

Results

Basic characteristic of the study cohort

Four hundred and twenty-eight children were recruited for this study. The recording of impedance and pH was well tolerated by the patients. After excluding two patients due to intolerance and a short monitoring time, 426 patients were included within the final cohort. After MII-pH monitoring was completed, a preliminary analysis was performed, and tracings were classified according to their quality and the presence of technical artifacts. None of the patients were treated for GERD before examination.

The median patient age at the time of MII-pH monitoring was 12 months (IQR: 6–39.5 months). Of the 426 patients, 292 (68.5%) patients were male, and 134 (31.5%) were female; 186 patients (43.7%) were infants whose ages ranged from 0 to12 months. There were 40 cases of premature birth (9.4%), 23 cases of neonatal complications (5.4%), and 24 cases of congenital malformations (5.6%), most of which were atrial septal. The number of recently diagnosed infections within 2 weeks before examination was 259 (60.8%) (Table 1). There were 129 patients (30.3%) in the acid GER group and 297 patients (69.7%) in the non-acid GER group. In acid GER group,97(67.4%) patients were male, and the median age was 36 months (IQR:10–63 months) which is higher than non-acid GER group with the median age 8 months(IQR:4-18 months) ($P < 0.01$).

Table 1 Demographic and clinical data of the study population ($N = 426$)

Total cases	426
Clinic information	
Sex (boy/girl)	292/134
Age (months)	12 (6–39.5)
Prematurity	40(9.4%)
Neonatal complications	23(5.4%)
Congenital malformation	24(5.6%)
Neurological comorbidity	15(3.5%)
Other chronic respiratory problems	95(22.3%)
Recent infections	259(60.8%)
Total recording time (hours)	24.1 (24–24.2)
Supine position time (hours)	11.5 (9.1–13.5)
Upright position time (hours)	12.2 (9.6–14.7)
pH metry	
Total reflux episodes	50 (19–140.25)
Reflux time > 5 min events	1 (0–8)
Maximum reflux time (minutes)	9.3 (3.1–37.1)
Reflux index	2.6 (0.8–9.2)
Impedance	
Reflux events in 24 h	110 (76–142)
Acid (%)	29.2 (12.8–57.1)
Weakly acidic (%)	57 (31.8–73)
Weakly alkaline (%)	5.6(0.8–13.8)
Liquid reflux (%)	24.5(12.5–38.9)
Gas reflux (%)	32.1(20.1–51.6)
Mixed reflux (%)	36.2(24.5–45.4)
SAP > 95%	59 (13.8%)

SAP Symptom-association probability

PH-metry data

The total recording duration was 24.1 h (24–24.2 h). Tracings were separately analyzed while the patients were in the supine (11.5 h [9.1–13.5 h]) and upright positions (12.2 h [9.6–14.7 h]). There were total 50 (IQR:19–140.25) acid reflux episodes occurring in 24 h and 1 (0–8) reflux event with a acid reflux duration > 5 min. The maximum reflux duration was 9.3 min (3.1–37.1 min). The RI was 2.6% (0.8–9.2%), and 129 (30.3%) children had RI > 7%.

Impedance data

Through the combined monitoring of impedance and pH, it was determined that the median number of reflux events occurring in 24 h was 110 (IQR: 76–142); the median percentages of total reflux events occurring in patients that involved acid reflux, weakly acidic reflux, and weakly alkaline reflux are 29.2% (IQR: 12.8%–57.1%), 57% (IQR: 31.8%–73.4%), and 5.6% (IQR: 0.8%–13.9%), respectively. Liquid was present in 24.5% (12.5–38.9%) of all reflux events, and gas was present in 32.1% (20.1–51.8%) of all reflux events. However, mixed gas–liquid reflux events accounted for the greatest proportion of total reflux events (36.4% [24.5–45.6%]). The correlation of reflux events and age in all patients was analyzed. We found that there was no relationship between age and the total number of reflux events ($r = 0.057$, $P = 0.234$) but a mild positive correlation was observed with acid reflux events ($r = 0.343$, $P < 0.05$). On analyzing the SAP for each patient, we found that for 59 children (13.8%), the SAP was > 95%. According to total reflux events form the impedance data, total 290 patients (68.1%) were MII positive and 136(31.9%) patients were MII negative. Patients with SAP > 95% in MII positive group (47[16.2%]) is higher than in MII negative group ($P < 0.05$) (Table 2).

Differences between upright and supine positions

There were 93 (IQR: 59–128) reflux events that occurred in the upright position, of which the percentages of acid reflux events, weakly acidic reflux events, and weakly alkaline reflux events were 33.1% (11.7–51.3%), 33.3% (13.5–52.5%), and 0% (0–4.3%), respectively. There were 18 (IQR: 8–34) reflux events that occurred in the supine

Table 2 Comparison of 24 h impedance monitoring parameters between MII-positive group and MII-negative group

	MII-positive group ***n*** **= 290(68.1%)**	**MII-negative group** ***n*** **= 136(31.9%)**	***P*** **value**
age(month)	13(6–46)	8(4–19.75)	< 0.05
Sex (boy/girl)	196/94	96/40	0.53
Total reflux episodes in pH-metry	58(20–152)	16(16–120.75)	< 0.05
RI > 7%	87(30%)	42(30.9%)	0.85
Total reflux events in MII	128(108–163)	64(47–79.25)	< 0.01
Acid (%)	29.37(13.46–57.15)	26.97(11.98–56.28)	0.73
Weakly acidic (%)	55.79(31.11–72.24)	59.79(32.98–77.76)	0.48
Weakly alkaline (%)	6.42(1.25–14.62)	2.65(0–13.27)	0.61
Liquid reflux (%)	24.77(15–38.67)	21.52(9.38–40.83	0.25
Gas reflux (%)	37.7(28.11–46.38)	30.63(16.67–41.43)	< 0.01
Mixed reflux (%)	30.12(19.21–47.76)	35.20(23.06–63.52)	< 0.01
SAP > 95%	47 (16.2%)	12 (8.8%)	< 0.05

SAP Symptom-association probability, *RI* Reflux index, *MII* Multichannel intraluminal impedance

position, of which the percentage of acid reflux events and weakly acidic reflux events were 4.4% (0.8–11.6%) and 5.5% (0–15.2%), respectively. Upright periods tended to be associated with the occurrence of a significantly higher number of total reflux events than supine periods ($P < 0.01$). A high number of both acid (33.1% [11.7–51.3%]) and weakly acidic reflux (33.3% [13.5–52.5%]) events occurred while the patients were in the upright position, whereas weakly acidic reflux (5.5% [0–15.2%]). was the predominant reflux type that occurred in the supine position. There was a significant difference in the physical properties of reflux between reflux events that occurred in the supine and upright positions: mixed reflux (29.7% [17.3–39.5%]) and gas reflux (25.3% [14.7–42.6%]) were dominant in the upright position, while liquid reflux (5.3% [1.7%-11.6%]) was dominant in the supine position (Table 3).

Differences between the infant and children groups

Pediatric patients were divided based on age into the infant (< 12 months; $n = 186$) and children (> 12 months; $n = 240$) groups. The infant group had higher rates of prematurity, chronic respiratory problems, and recent infections than the children group ($P < 0.01$). There was no significant difference in the proportion of neonatal complications or congenital malformations between the groups. Through pH monitoring, we found that, the infant group had significantly lower total reflux episodes, reflux episodes in the upright position, and reflux episodes in the supine position than did the children group; they also had a lower number of acid reflux events > 5 min and maximum reflux time ($P < 0.01$). Through impedance monitoring, we found that there was no difference between the two groups regarding reflux events occurring in 24 h ($P = 0.825$). With respect to the chemical properties of reflux, weakly acidic reflux was predominant in the infant group (67.8% [52.1–81.4%]), while in the children group, acid reflux was predominant (44.3% [20.7–63.2%]). The occurrence of mixed reflux in the infant group 38.7 [28.8–49.5] was significantly higher than that in the children group 32.8

Table 3 Comparison of 24 h impedance monitoring parameters between upright and supine positions

				Chemical properties of reflux (%)			**Physical properties of reflux (%)**		
	Percentage of reflux time in total time (%)	**Reflux events in impedance**	**Reflux episodes in pH metry**	**Acid**	**Weakly acidic**	**Weakly alkaline**	**Liquid**	**Gas**	**Mixed**
Upright position	6.1 (1.7–28.7)	93 (59–128)	38 (13–95)	33.1 (11.7–51.3)	33.3 (13.5–52.5)	0 (0–4.3)	15.3 (6.7–26.3)	25.3 (14.7–42.6)	29.7 (17.3–39.5)
Supine position	2 (0.3–17.9)	18 (8–34)	7 (2–33)	4.4 (0.8–11.6)	5.5 (0–15.2)	0 (0–0)	5.3 (1.7–11.6)	3.9 (1.2–8.9)	3.1 (0.9–7.3)
P-value	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Table 4 Comparison of 24 h impedance monitoring parameters between infant and children groups

	Infant *n* = 168	Children *n* = 258	*p*-value
Age (months)	5 (3–7)	36 (17–64.5)	< 0.01
Sex (boy/girl)	135/33	157/101	0.06
Prematurity	29(17.3%)	11(4.3%)	< 0.01
Neonatal complications	15(9.0%)	8(3.1%)	0.14
Congenital malformation	12(7.1%)	12(4.7%)	0.28
Neurological comorbidity	10(6.0%)	5(1.9%)	0.43
Other chronic respiratory problems	66(31.1%)	29(11.2%)	< 0.01
Recent infections	170(80.2%)	89(34.5%)	< 0.01
pH metry			
Total reflux episodes	31 (12–69)	96(30–191)	< 0.01
Reflux episodes in upright position	21 (9–56)	68(23–137)	< 0.01
Reflux episodes in supine position	5(1–18)	14 (3–44)	< 0.01
Reflux time > 5 min events	1(0–4)	3(0–16)	< 0.01
Maximum reflux time (minutes)	6.55(2.8–19.5)	13.45(4.0–59.8)	< 0.01
RI > 7%	35(16.5%)	94(36.4%)	< 0.01
Impedance			
Reflux events in 24 h	110(84–140.3)	110.5(72–146)	0.83
Acid (%)	19.9(8.1–37.6)	44.3(20.7–63.2)	< 0.01
Weakly acidic (%)	67.8(52.1–81.4)	40.8(26.2–59.8)	< 0.01
Weakly alkaline (%)	2.4(0–10.1)	8.1(2.6–18.1)	< 0.01
Liquid reflux (%)	22.6(12.2–38.3)	25.1(13.6–39.8)	0.3
Gas reflux (%)	30.7(20.7–47.8)	33.3(19.6–57.7)	0.38
Mixed reflux (%)	38.8(28.8–49.5)	32.8(21.4–42.6)	< 0.01
Cough episodes	11 (5–21)	6(2–14)	< 0.01
Reflux positive cough episodes	0 (0–2)	1(0–2)	0.066
SAP > 95%	32(15.1%)	27(10.5%)	0.486

SAP Symptom-association probability, *RI* Reflux index

[21.4–42.6] ($P < 0.01$). There was no difference in SAP between the two groups ($P = 0.486$) (Table 4).

Differences between the acid GER and non- acid GER groups

Patients were divided into an acid GER (RI > 7%;$n = 129$) and non-acid GER (RI ≤ 7%; $n = 297$) group which is solely based on based on pH monitoring. The proportion of recent infection in the non-acid GER group (66%) was significantly higher than that in the acid GER group (51.2%) ($P < 0.01$). There were no significant differences between the two groups in terms of prematurity, congenital malformation, and other chronic respiratory problems. Furthermore, there was no difference in the total recording time between the two groups ($P = 0.762$). Through pH monitoring, we found that the acid GER group had significantly higher total reflux episodes (200[150–279]), reflux episodes in the upright position (139[86–215]), and reflux episodes in the supine position (41[21–72]) than did the non-acid GER group. The acid GER group also had a higher acid reflux events > 5 min episodes (17 [7–25]) and maximum reflux time (62.5[30.9–146.3]) ($P < 0.01$). However, through impedance monitoring, we found that there was no difference between the two groups regarding reflux events occurring in 24 h ($P = 0.85$). With respect to the chemical properties of reflux, most reflux events in the acid GER group involved acid reflux (64.7% [51.5–76.4%]). The proportion of total reflux events in the non-acid GER group that involved weakly acidic reflux (65.7%[52.2–79.7%]) and alkaline reflux (6.8%[1.1–19.7%]) was significantly greater than that in the acid GER group ($P < 0.01$). With respect to the physical properties of reflux, the percentage of reflux events that involved gas reflux was higher in the non-acid GER group (33.8%[23.7–54.8%]) than in the acid GER group (24.7%[14.6–42.7%]) ($P < 0.01$). The reflux-positive cough episodes were higher in the acid GER (1[0–4]) group than in the non-acid GER group (0[0–1]) ($P < 0.01$). With respect to SAPs, there was no

Table 5 Comparison of 24 h impedance monitoring parameters between acid GER and non-acid GER groups

Group	Acid GER	Non-acid GER	*P*-value
Sex (boy/girl)	87/42	205/92	0.74
Age (months)	36(10–63)	8(4–18)	< 0.01
Prematurity	9(7%)	31(10.4%)	0.28
Neonatal complications	8(6.2%)	15(5.1%)	0.64
Congenital malformation	5(3.9%)	19(6.4%)	0.5
Neurological comorbidity	4(3.1%)	11(3.7%)	0.21
Other chronic respiratory problems	23(17.8%)	72(24.2%)	0.16
Recent infections	66(51.2%)	196(66%)	< 0.05
pH metry			
Total reflux episodes	200(150–279)	30(13–62)	< 0.01
Reflux episodes in upright position	139(86–215)	21(10–49)	< 0.01
Reflux episodes in supine position	41(21–72)	3(1–10)	< 0.01
Reflux time > 5 min episodes	17(7–25)	0(0–2)	< 0.01
Maximum reflux time (minutes)	62.5(30.9–146.3)	4.7(2.3–10.3)	< 0.01
Impedance			
Reflux events in 24 h	110(69–149)	110(80–140)	0.85
Acid (%)	64.7(51.5–76.4)	19.3(8.0–33.1)	< 0.01
Weakly acidic (%)	28.2(18.6–38.4)	65.7(52.2–79.7)	< 0.01
Weakly alkaline (%)	4.0(0–8.3)	6.8(1.1–19.7)	< 0.01
Liquid reflux (%)	32.1(20.1–45.8)	21.6(10.8–35.8)	< 0.01
Gas reflux (%)	24.7(14.6–42.7)	33.8(23.7–54.8)	< 0.01
Mixed reflux (%)	37.1(25.3–46.0)	35.3(23.9–44.6)	0.5
Cough episodes	6(3–15)	9(5–19)	0.013
Reflux positive cough episodes	1(0–4)	0(0–1)	< 0.01
SAP > 95%	17(13.2%)	42(14.1%)	0.88

GERD Gastro-esophageal reflux disease, *SAP* Symptom-association probability

significant difference between the two groups ($P = 0.88$) (Table 5).

Discussion

To the best of our knowledge, this was the largest study involving MII-pH monitoring for evaluating the association between chronic cough and gastroesophageal reflux in children. Using this technique, we can detect previously overlooked gastroesophageal reflux events in infants and young children with chronic cough. Our results showed that more than 30.3% of the enrolled children with chronic cough were associated with acid reflux, and impedance monitoring also detected significant amounts of weakly acidic reflux events in the remaining children, highlighting the importance of 24 h MII-PH monitoring in evaluating these children. Using an accurate diagnostic tool, children with gastroesophageal-reflux-related chronic cough can be accurately identified, and their treatment can be improved.

Cough is one of the most common symptoms of respiratory diseases in children, and chronic cough has several causes. Reflux-related cough is caused by direct irritation of the tracheobronchial tree after aspirating gastric contents into the airway; it may also be caused by stimulation of the esophageal-bronchial neural cough reflex [13]. Changes in the pressure gradient between the abdominal and thoracic cavities that occur during cough events may also lead to a cycle of cough and reflux [14]. Accurately diagnosing an individual with chronic cough caused by gastroesophageal reflux is a major challenge [15], and to the best of our knowledge, only a few studies involving MII-pH monitoring in patients with chronic cough have been performed previously [15].

A study by Rosen and Nurko showed that in children with various respiratory symptoms (including chronic cough), cough events in 37.6% of children were related to gastroesophageal reflux [16]. The findings of a study by Ghezzi et al. suggested a 78.3% correlation between cough and gastroesophageal reflux [17]. However, in our study, we found that more than 30.3% of the included children with chronic cough related to acid reflux. Discrepancies among study findings might have occurred due to differences in sample sizes and recording methodologies. The American College of Gastroenterology

guidelines for the diagnosis and treatment of GERD define GERD as "chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus" [18]. The diagnosis of cough caused by reflux may be challenging because many children do not exhibit typical symptoms of reflux. Symptoms such as heartburn, acid regurgitation, dysphagia in older children, or agitation and food refusal in toddlers and infants are not specific to GERD and are, therefore, a diagnostic challenge. In cases involving patients with atypical GERD symptoms, respiratory manifestations have been found to be either the only significant manifestation or the most significant manifestation of GERD [19]. In one of the largest pediatric studies regarding chronic cough in children, the "big three" causes of chronic cough in adults (asthma, upper airway cough syndrome, and GERD) were found in a small proportion of children ($\leq$10% of the study cohort) [20]. This might have been due to the lack of diagnostic tools for GERD in children and the lack of awareness regarding gastroesophageal reflux cough.

The most commonly used method to confirm the presence of GERD is ambulatory 24-h esophageal pH monitoring, which can only be used to evaluate acid reflux events [19]. The development of MII-pH monitoring is an addition to pH monitoring. MII-pH monitoring allows for a more comprehensive evaluation of different aspects of GERD than pH monitoring; this technique is based on a combination of pH-metry and the evaluation of esophageal contents using multiple channels, which allows for the description and evaluation of acid and non-acid reflux events, the physical and chemical properties of reflux, and the association between symptoms [21, 22].

The role of MII-pH has gradually increased in the past few years, especially for the evaluation of children. Children receiving enteral nutrition through continuous or bolus regimens can only be accurately evaluated through MII-pH monitoring because in these children, the majority of gastroesophageal reflux events involve non-acid reflux due to the buffering effect of feedings [7]. MII-pH monitoring currently represents the gold standard diagnostic technique for measuring acid and non-acid GERD and symptom association [23]. However, as MII-pH monitoring is expensive, the technique is only available in a limited number of centers [5]. Pavić et al. demonstrated that pH-metry alone did not show an association between acid reflux and cough in children; however, a relationship between weakly acidic reflux and cough was described [24]. Their results suggest that the use of pH-metry alone may be insufficient to identify reflux-related cough in children, especially young children. This is consistent with our results, acid reflux events detected by pH-metry in infants group was less than that in older group, whereas the infant group had more weakly acid and weakly alkaline reflux detected by MII; however, no difference in reflux events was detected between the two groups by impedance. This may be because a significant number of gastroesophageal reflux events occurring in infants involve non-acid reflux (pH > 4). However, it appears that extraesophageal symptoms, such as laryngitis, pharyngitis, asthma, cough, and dental erosion, may be caused by both acid (pH < 4) and non-acid reflux (pH > 4) [25, 26]. In our study, the acid GER and non-acid GER groups showed significant differences with respect to the occurrence of acid reflux; however, there was no difference with respect to impedance events. Similar results have been reported in other studies; in a past study involving eight children for whom the results of pH monitoring were normal, abnormal impedance events could still be detected, and the impedance events mainly involved gas and mixed gas–liquid reflux [27]. In another study, pH and impedance were monitored in 27 children with asthma, and non-acid reflux events accounted for half of the reflux events detected through MII-pH monitoring [28]. This indicates that with respect to the diagnosis of GERD, the diagnostic sensitivity of MII-pH monitoring is significantly higher than that of pH monitoring [29]. Another study showed that age is positively correlated with acid reflux and negatively correlated with weakly acidic reflux. This is consistent with our research with the result that the infants with weak acidic reflux are significantly higher than the children [30]. A large proportion of reflux events in children, especially those in infants, involve gas reflux and weakly alkaline reflux, and the evaluation of such patients through only pH monitoring may lead to misdiagnoses. The significant effect of non-acid reflux on the development of respiratory symptoms in children was previously reported by Wenzel et al. in their study involving 22 infants who underwent MII-pH monitoring [31].

Similarly, the findings of the present study regarding relatively younger children included in the non-acid GER group suggest that children who have chronic cough at a young age tend to have non-acid reflux, which can only be detected through impedance monitoring. Therefore, physicians should be aware of the limitations of pH monitoring in pediatric populations [26].

Blondeau et al. found that there was a significant correlation between gastroesophageal reflux and cough in 26 children, which was mainly caused by weakly acidic reflux [32]. In a previous study involving 45 children with chronic cough, 158 cough episodes were related to reflux events; of these, 53 involved non-acid reflux, which might not have been identified if only pH monitoring had been used [33]; these results are consistent with the results of our study demonstrating that the proportion of reflux events that involve weakly acidic reflux was significantly

greater than the proportion of reflux events that involve acid reflux. In addition, Pavić et al. confirmed that weakly acidic reflux is more significantly associated with cough than acid reflux and that children < 2 years of age have a significantly higher number of cough episodes associated with acid and weakly acidic reflux. [24] This is consistent with our findings. Weakly acidic reflux occurs most commonly in younger children due to physiological reasons; during infancy, gastric contents are buffered by frequent feeding, and the composition and volume of each feed differ [34]. One hypothesis is that small amounts of proximal weakly acidic reflux cannot stimulate acid- and volume-sensitive esophageal receptors, which play a significant role in providing protection against aspiration [35].

The occurrence of reflux is more common when babies are in the upright position than in the supine position, and the findings of our study are consistent with this fact; the increased occurrence of reflux in the upright position may be caused by increased intra-abdominal pressure in babies [36]. Our study suggested that both acid and non-acid reflux events mainly occur in children when they were in the upright position; this may also have been caused by eating, which is often carried out in the upright position. With respect to the physical properties of reflux, our study showed that reflux events mainly involved gas and mixed gas–liquid reflux, which is difficult to detect through pH monitoring. In children, the presence of these types of reflux may render anti-reflux treatment ineffective.

SAP is commonly used to analyze the relationship between symptoms and gastroesophageal reflux [37]. The findings of our study indicate that 13.8% of all included patients and 17% of patients in the acid GER group were SAP positive. These values represent a relatively small proportion of the total number of patients. Borrelli et al. reported that only 17 of 45 children with unexplained chronic cough had a positive SAP and that asymptomatic and non-acid gastroesophageal reflux may be important [33]. The findings of another study showed that there is a low correlation between cough and reflux events in children [38]. The relationship between gastroesophageal reflux and cough is very complicated, which makes it difficult to analyze and interpret associated results. The SAP only reflects the cough episodes and symptoms that occur after 2 min of the occurrence of a reflux event [37]. It has been reported that cough episodes that occur in individuals within 2 min of the occurrence of a reflux event only account for 56–81% of the total cough episodes that occur in them [19]. Patients often omit the recording of the occurrence of cough episodes or mislabel the same cough event; therefore, SAP calculations are often not very accurate. As under-reporting of symptoms may lead to false negative results, a past study of 20 children found that while only 48% of all cough episodes were reported by children and/or their parents, 94% of all cough episodes were detected by recording intra-esophageal pressure [39]. Further, the accuracy of symptom records is limited, which affects the relevance of events and reflux [40]. As chronic cough itself can also cause gastroesophageal reflux, this increases the difficulty of determining the causal relationship between cough and reflux [41]. And our study shows that 14.1% of children in non-acid GER group were SAP positive, which means non-acid reflux is also associated with chronic cough.

These factors indicate that anti-acid therapy may not be effective for the treatment of cough associated with gastroesophageal reflux, which is consistent with the findings of other studies. A meta-analysis showed that proton pump inhibitors were not efficacious for cough associated with gastroesophageal reflux symptoms in young children [13]. Medical treatment with acid-suppression therapy and dietary and lifestyle modifications are recommended in clinical guidelines for children with chronic cough and typical symptoms of GERD. Based on our results, we suggest that proton pump inhibitors are administered to children in whom a significant proportion of reflux events involve acid reflux; however, for infants who do not have acid reflux, treatment should be based on the introduction of appropriate dietary and lifestyle changes.

This study has some limitations worth noting. First, symptoms were recorded by the family members of the included patients, which might have resulted in inaccuracies. Second, children were not followed up to evaluate treatment outcomes and prognosis. In the future, we will do a better job of following up with the children and improve the clinical data.

Conclusions

In conclusion, the use of 24 h MII-pH monitoring in this study improved our understanding of children with reflux-related chronic cough. It can identify weak acidic reflux, weak alkaline reflux and reflux events with different physical properties, which can explain the relationship between GER and chronic cough more comprehensively. The high proportion of non-acid reflux events in children identified in this study highlights the need for increased awareness among healthcare providers and the importance of being cautious about the treatment of reflux and reflux-related cough with antacid medications. It provides new approach for exploring the etiology, diagnosis and treatment of children with chronic cough.

Acknowledgements
We appreciate the participation of the children and their families. We would like to thank Editage (www.editage.com) for English language editing.

Authors' contributions
Junhua Shu and Danna Tu is acting as the submission's guarantor. Zhaoxuan Huang, Shan Gao and Junhua Shu performed the research. Shan Gao, Li Gu, Di Zhang, Lingzhi Yan, Shanshan Shang and Guirong Wang collected the data. Yi Gan analysed the data. Yi Gan, Xiaoqin Zhou, Danna Tu and Junhua Shu designed the research study, Yi Gan and Junhua Shu wrote the paper. All authors approved the final version of the article, including the authorship list.

Funding
This research was supported by the Hubei Provincial Natural Science Foundation of China (Grant Number: 2022CFB401 and Grant Number:2021CFB558).

Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province (2022IEC105). All methods were performed in accordance with the relevant guidelines and regulations. The parents or guardians of all participants provided written informed consent to take part in the present study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pediatric, Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology, Wuhan City, Hubei Province, P.R. China.

Received: 21 April 2023 Accepted: 26 July 2024
Published online: 22 August 2024

References

1. Chang AB, et al. Use of management pathways or algorithms in children with chronic cough: CHEST guideline and expert panel report. Chest. 2017;151:875–83.
2. Irwin RS, Richter JE. Gastroesophageal reflux and chronic cough. Am J Gastroenterol. 2000;95(suppl):S9–14.
3. Chang AB, et al. Chronic cough and gastroesophageal reflux in children: CHEST guideline and expert panel report. Chest. 2019;156:131–40.
4. Rosen R, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American society for pediatric gastroenterology, hepatology, and nutrition and the European society for pediatric gastroenterology, hepatology, and nutrition. J Pediatr Gastroenterol Nutr. 2018;66:516–54.
5. from guidelines to clinical practice. Gonzalez Ayerbe, J. I., Hauser, B., Salvatore, S. & Vandenplas, Y. Diagnosis and management of gastroesophageal reflux disease in infants and children. Pediatr Gastroenterol Hepatol Nutr. 2019;22:107–21.
6. Gyawali CP, et al. Modern diagnosis of GERD: the Lyon consensus. Gut. 2018;67:1351–62.
7. Quitadamo P, et al. Esophageal pH-impedance monitoring in children: position paper on indications, methodology and interpretation by the SIGENP working group. Dig Liver Dis. 2019;51:1522–36.
8. Strobel CT, et al. Correlation of esophageal lengths in children with height: application to the Tuttle test without prior esophageal manometry. J Pediatr. 1979;94:81–4.
9. Blondeau K, et al. Improved diagnosis of gastro-oesophageal reflux in patients with unexplained chronic cough. Aliment Pharmacol Ther. 2007;25:723–32.
10. Vandenplas Y, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.
11. Salvatore S, et al. Distress in infants and young children: don't blame acid reflux. J Pediatr Gastroenterol Nutr. 2020;71:465–9.
12. Pilic D, et al. Detection of gastroesophageal reflux in children using combined multichannel intraluminal impedance and pH measurement: data from the German pediatric impedance group. J Pediatr. 2011;158:650–4.
13. Shields MD, et al. BTS guidelines: recommendations for the assessment and management of cough in children. Thorax. 2008;63(suppl 3):iii1–15.
14. de Benedictis FM, Bush A. Respiratory manifestations of gastro-oesophageal reflux in children. Arch Dis Child. 2018;103:292–6.
15. Sifrim D, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. Gut. 2005;54:449–54.
16. Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. Am J Gastroenterol. 2004;99:2452–8.
17. Ghezzi M, et al. Weakly acidic gastroesophageal refluxes are frequently triggers in young children with chronic cough. Pediatr Pulmonol. 2013;48:295–302.
18. DeVault KR, Castell DO, American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005;100:190–200.
19. Gonçalves ES, et al. Multichannel intraluminal impedance-pH and psychometric properties in gastroesophageal reflux: systematic review. J Pediatr (Rio J). 2020;96:673–85.
20. Marchant JM, et al. Evaluation and outcome of young children with chronic cough. Chest. 2006;129:1132–41.
21. Mousa H, Hassan M. Gastroesophageal reflux disease. Pediatr Clin North Am. 2017;64:487–505.
22. Frazzoni M, et al. Impedance-pH monitoring for diagnosis of reflux disease: new perspectives. Dig Dis Sci. 2017;62:1881–9.
23. Davies I, Burman-Roy S, Murphy MS, Guideline Development Group. Gastro-oesophageal reflux disease in children: NICE guidance. BMJ. 2015;350:g7703.
24. Pavić I, Čepin-Bogović J, Hojsak I. The relationship between gastroesophageal reflux and chronic unexplained cough in children. Clin Pediatr (Phila). 2016;55:639–44.
25. Durazzo M, Lupi G, Cicerchia F, et al. Extra-esophageal presentation of gastroesophageal reflux disease: 2020 update. J Clin Med. 2020;9:2559.
26. Wenzl TG. Evaluation of gastroesophageal reflux events in children using multichannel intraluminal electrical impedance. Am J Med. 2003;115(suppl. 3A):161S-165S.
27. Soyer T, et al. Results of multichannel intraluminal impedance pH metry in symptomathic children with normal pH metry findings. Eur J Pediatr Surg. 2014;24:514–8.
28. Condino AA, et al. Evaluation of gastroesophageal reflux in pediatric patients with asthma using impedance-pH monitoring. J Pediatr. 2006;149:216–9.
29. Safe M, Cho J, Krishnan U. Combined multichannel intraluminal impedance and pH measurement in detecting gastroesophageal reflux disease in children. J Pediatr Gastroenterol Nutr. 2016;63:e98–106.
30. Cresi F, Cester EA, Salvatore S, et al. Multichannel intraluminal impedance and pH monitoring: a step towards pediatric reference values. J Neurogastroenterol Motil. 2020;26:370–7.
31. Wenzl TG, et al. Gastroesophageal reflux and respiratory phenomena in infants: status of the intraluminal impedance technique. J Pediatr Gastroenterol Nutr. 1999;28:423–8.
32. Blondeau K, et al. The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings. Pediatr Pulmonol. 2011;46:286–94.
33. Borrelli O, et al. Role of gastroesophageal reflux in children with unexplained chronic cough. J Pediatr Gastroenterol Nutr. 2011;53:287–92.

34. López-Alonso M, et al. Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux. Pediatrics. 2006;118:e299–308.
35. Jadcherla SR, et al. Esophago-glottal closure reflex in human infants: a novel reflex elicited with concurrent manometry and ultrasonography. Am J Gastroenterol. 2007;102:2286–93.
36. Omari TI, et al. Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. J Pediatr. 2004;145:194–200.
37. Weusten BL, et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology. 1994;107:1741–5.
38. Chang AB, et al. An objective study of acid reflux and cough in children using an ambulatory pH metry-cough logger. Arch Dis Child. 2011;96:468–72.
39. Rosen R, et al. Intraesophageal pressure recording improves the detection of cough during multichannel intraluminal impedance testing in children. J Pediatr Gastroenterol Nutr. 2014;58:22–6.
40. Sifrim D, et al. Review article: acidity and volume of the refluxate in the genesis of gastro-oesophageal reflux disease symptoms. Aliment Pharmacol Ther. 2007;25:1003–17.
41. Pandolfini C, Impicciatore P, Bonati M. Parents on the web: risks for quality management of cough in children. Pediatrics. 2000;105:e1.

Publisher's Note