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The Role of Combined Multichannel Intraluminal Impedance-pH Monitoring in Infants with Brief, Resolved, Unexplained Events

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: Data on the relationship between gastroesophageal reflux (GER) and brief resolved unexplained events (BRUE) in infants is scarce. The aim of this study was to identify the characteristics of combined multichannel intraluminal impedance-pH (MII-pH) monitoring in infants who have experienced BRUE.
Methods: We conducted a prospective study of infants who were hospitalized on account of BRUE and required 24-hour MII-pH monitoring.
Results: Twenty-one infants (mean age, 4.7 months; range, 0.9–8.9 months; male/female, 11/10) participated in this study. BRUE symptoms associated with GER were found in 10 infants (47.6%). Based on the RI on pH-metry alone, only 7 (33.3%) infants were diagnosed with GERD. More than 100 GER episodes detected by MII were found in 10 (47.6%) infants. Nineteen percent of infants were diagnosed with GERD based on both pH and MII.
Conclusion: Both acid and non-acid reflux seem to play a significant role in the pathogenesis of GER-related BRUE in infants.

Keywords: Apnea; Infant, newborn; Gastroesophageal reflux

INTRODUCTION

Gastroesophageal reflux (GER) is common in preterm and term infants [1]. Harmful consequences of GER, called GER disease (GERD), have been associated with different manifestations such as obstructive apnea, oxygen desaturation, stridor, and wheezing [2,3]. Apneas and brief resolved unexplained events (BRUE), irrespective of their nature, have been proposed to be GER-induced, although evidence is limited and inconclusive [4]. BRUE, previously known as Apparent Life Threatening event (ALTE), is described as a sudden, brief, and resolved episode in an infant that includes one or more of the following features: cyanosis or pallor, absent, decreased, or irregular breathing; marked change in tone (hyper- or hypotonia); and altered level of responsiveness. Criteria for low risk BRUE are

as follows: age >60 days or born at gestational age ≥32 weeks and current postconceptional age is ≥45 weeks, if premature; occurrence of only one BRUE (no prior BRUE, and BRUE did not occur in clusters); duration of BRUE <1 minute; no cardiopulmonary resuscitation by a trained medical provider was required; no concerning historical features (social risk factors for child abuse, respiratory illness or exposure, recent injury, other symptoms in days preceding the event (fever, fussiness, diarrhea, or decreased intake), administration or access to medications, history of episodic vomiting or lethargy, developmental delay or congenital anomalies, and family history of BRUE or sudden unexplained death in a sibling; and no concerning physical examination findings (any signs of injury, including bleeding, bruising or bulging anterior fontanel; altered sensorium; fever or toxic appearance; respiratory distress; heart murmur or gallop; decreased pulses; hepatomegaly or splenomegaly; and abdominal distension or vomiting) [5]. In neonates and small infants, nonacid GER, rather than acidic GER, plays a major role in causing the symptoms [2]. Nonacid GER can only be detected using multichannel intraluminal impedance with esophageal pH monitoring (MII-pH) and should, therefore, be a method of choice. However, few studies have assessed the association between GER and apnea/BRUE in small infants [2,6-8]. Therefore, the aim of this study was to identify the characteristics of MII-pH monitoring in infants who had experienced BRUE.

MATERIALS AND METHODS

Study design

Infants hospitalized due to ALTE or high-risk BRUE and who were referred for 24-hour MII-pH monitoring from January 2012 to September 2017 and who were followed up for 12 months were prospectively included in this study. The indication and procedure was explained and discussed with the child's parents or caregivers before inclusion in the study, and only those children who fulfilled the inclusion criteria and whose parents or caregivers signed the informed consent were included accordingly.

The inclusion criteria were BRUE and age before 12 months. BRUE was defined as a sudden, brief, and now resolved episode that included one or more of the following features: cyanosis or pallor; absent, decreased, or irregular breathing; marked change in tone (hyper- or hypotonia); and altered level of responsiveness [5]. Irregular breathing/apnea is a symptom of BRUE and occurs when the infant has pauses in breathing for no more than 10 seconds at a time, followed by a series of rapid, shallow breaths [9].

Infants with proven neurological impairment, heart and pulmonary congenital abnormalities, anomalies of the upper gastrointestinal tract, and craniofacial abnormalities were accordingly excluded from the study.

All included children underwent the same diagnostic protocol, which included past medical history, BRUE details on initial presentation, feeding history, physical examination and growth parameters, cardio-respiratory monitoring (CR) during hospitalization, and 24-hour MII-pH monitoring. We defined preterm infants as those with a gestational age of <37 weeks. Heart rate, transcutaneous blood oxygen saturation, and respiratory rate were measured during CR and MII/pH monitoring by a pulse-oximetry sensor placed on the right wrist or foot and three cardiac electrodes placed on the chest, and airflow monitoring by a thermistor for the diagnosis of obstructive apnea. The occurrence of apnea (to >10 seconds), bradycardia

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(to <100 beats/min for ≥5 seconds), or desaturation (to <85% for ≥5 seconds) were accordingly recorded by the medical staff upon sounding of the alarm [10,11]. CR tracings were "visually" analyzed by a trained operator blinded to the MII/pH tracings.

This study was approved by the Ethical Committee of Children's Hospital Zagreb, Croatia (protocol number: 02-26/10-5-15).

24-hour MII-pH monitoring procedure

All children underwent 24-hour MII-pH monitoring using an MII-pH ambulatory system (Ohmega; Laborie, Enschede, The Netherlands), according to a previously published protocol [12-15]. Parents/guardians were instructed on how to record BRUE symptoms (irregular breathing/apnea, cyanosis or pallor, altered level of responsiveness, choking, marked change in muscle tone, back arching, gagging, vomiting, and coughing) during the 24-hour MII-pH monitoring. The impedance recordings were analyzed using criteria described in a consensus statement on indications, methodology, and interpretation of combined MII-pH monitoring in children [16]. Full-column reflux was defined as an episode that reached the highest pair of impedance sensors.

GERD was defined as >100 total GER episodes in infants based on impedance results and as a reflux index (RI) >10% in infants based on pH-metry [17,18]. The symptom index (SI reported as %) was defined as the percentage of GER-associated symptoms divided by the total number of symptoms. Normal value is <50%. The symptom sensitivity index (SSI reported as %) was defined as the percentage of symptom-associated GER events divided by the total number of GER events. Normal value is <10%. The symptom association probability (SAP, reported as %) was defined as the statistical means (Fisher exact test) to calculate the probability that the recorded symptoms and GER events were related accordingly. The normal value was <95% [16]. A window period of 30 seconds was used to consider the association between the BRUE symptoms and GER events.

After careful evaluation of the patient, the treatment plan was chosen in accordance with the joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition [19] and standardized in-house procedures. Patients were followed up for 12 months, and the treatment outcomes were evaluated accordingly.

Outcomes

The primary outcome was to determine the MII-pH characteristics of the infants who presented with BRUE.

Secondary outcomes were: (1) to compare pH and MII characteristics between premature and term born infants; (2) to compare pH and MII characteristics between infants with positive and negative SAP; and (3) to assess treatment used and symptom improvement.

Statistics

Differences between continuous variables were assessed using the Mann–Whitney test due to the small sample size and non-normal distribution. To compare categorical variables, the χ^2 test was used. Correlation analysis was performed using Spearman's correlation test. Statistical significance was set at $p<0.05$. Statistical analysis was performed using IBM SPSS Statistics for Window, Version 24.0 (IBM Co., Armonk, NY, USA) statistical software.

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RESULTS

Patients

During the study period, 21 infants were included, with a mean age of 4.7 months (range, 0.9–8.9); 11 (52.4%) were male. Cohort 9 (42.9%) were born prematurely. The mean weight at diagnosis was 5.64 kg (range, 2.5–10 kg). Overall, 19 (90.5%) infants had pathological CR monitoring (13 of them were later diagnosed with GERD based on the MII study).

Primary outcomes

During MII-pH monitoring, bradycardia was noted in 13 (61.9%), desaturation in 14 (66.7%), and coughing in one (4.8%) infant. During MII-pH monitoring, 12 (57.1%) children experienced BRUE symptoms recorded by parents (irregular breathing/apnea, cyanosis or pallor, altered level of responsiveness, choking, marked change in muscle tone, back arching, gagging, vomiting, and coughing). A total of 365/617 (59.1%) BRUE symptoms were recorded by parents related to reflux. BRUE symptoms associated with GER were found in 10 infants (47.6%). The characteristics of the MII-pH study are presented in **Table 1**. No complications were noted during or after the MII-pH procedure.

Based on the RI (>10%) on pH-metry, only 7 (33.3%) infants were diagnosed with GERD. More than 100 GER episodes detected by MII were found in 10 (47.6%) infants. Nineteen percent (4/21) of infants had GERD diagnosed using both pH and MII. There was no correlation between the total number of full column GER episodes and the probability of GER being associated with BRUE (coefficient 0.136, p=0.557).

Secondary outcomes

There was no difference between prematurely born infants and term infants in the rate of GER based on pH monitoring alone (4/9 vs. 3/12; p=0.350) and based on association scores on the MII study alone (4/9 vs. 7/12; p=0.528). Among all reflux episodes, there was a significantly higher number of proximal weakly acidic GER and proximal non-acidic GER (**Table 2**) in term-born infants. There was no difference between infants with positive and negative SAP in the combined multichannel intraluminal impedance-pH findings (**Table 3**).

Treatment

Cow's milk elimination diet was introduced in 7 (33.3%) and medication therapy in 9 (42.9%) children, proton pump inhibitor (PPI) in 4, and prokinetics in 5 children respectively. During the follow-up of 12 months in 15 (71.4%) infants, symptoms improved significantly more in

Table 1. Primary outcome measures of the included patients

Variable	Value (n=21)
Reflux episodes on pH monitoring	21 (0–417)
Reflux index	2.9 (0–32)
Acidic reflux episodes	10 (0–35)
Weakly acidic reflux episodes	42.5 (0–143)
Non-acidic reflux episodes	42.5 (0–144)
Proximal acidic reflux episodes	4.5 (0–24)
Proximal weakly acidic reflux episodes	26 (0–134)
Proximal non-acidic reflux episodes	26 (0–134)
SI	26.8 (0–100)
SSI	2.9 (0–25)
SAP	97.2 (0–100)

Values are presented as median (range).
SI: symptom index, SSI: symptom sensitivity index, SAP: symptom association probability.

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Table 2. Difference between term and preterm infants in the age and combined multichannel intraluminal impedance-pH findings

Variable	Prematurely born (n=9)	Term born (n=12)	*p*-value
Age (mo)	4.8 (1.1–8.9)	4.2 (0.9–8.9)	0.917
Reflux episodes on pH monitoring	28 (0–417)	21 (0–101)	0.310
Reflux index	2.9 (0.1–32)	2.1 (0–22.3)	0.095
Acidic reflux episodes	12 (0–25)	10 (0–35)	0.754
Weakly acidic reflux episodes	14 (0–103)	46.5 (16–143)	0.058
Non-acidic reflux episodes	14.5 (0–103)	46.5 (16–144)	0.060
Proximal acidic reflux episodes	3 (0–20)	5.5 (0–24)	0.554
Proximal weakly acidic reflux episodes	6 (0–65)	34 (3–134)	0.034
Proximal non-acidic reflux episodes	6.5 (0–65)	34 (3–134)	0.034
SI	10.1 (0–75)	33.1 (0–100)	0.422
SSI	2 (0–22)	3.6 (0–25)	0.602
SAP	49.8 (0–100)	97.2 (0–100)	0.651

Values are presented as median (range).
SI: symptom index, SSI: symptom sensitivity index, SAP: symptom association probability.

Table 3. Difference between infants with SAP positive and negative result in combined multichannel intraluminal impedance-pH findings

Variable	SAP >95% (n=11)	SAP ≤95% (n=10)	*p*-value
Age (mo)	7 (2–9)	3 (2–4)	0.008
Reflux episodes on pH monitoring	29 (0–417)	19 (1–23)	0.426
Reflux index	8.2 (0–32)	1.4 (0.1–3.1)	0.314
Acidic reflux episodes	12 (0–35)	23 (0–25)	0.973
Weakly acidic reflux episodes	46 (9–105)	86 (0–143)	0.251
Non-acidic reflux episodes	46 (9–105)	86 (0–144)	0.251
Proximal acidic reflux episodes	8 (0–20)	23 (0–24)	0.705
Proximal weakly acidic reflux episodes	29 (4–98)	77 (0–134)	0.387
Proximal non-acidic reflux episodes	29 (4–98)	77 (0–134)	0.387
Symptoms	46 (3–104)	0 (0–8)	0.011
GER related symptoms	24 (2–84)	0 (0–3)	0.011

Values are presented as median (range).
SAP: symptom association probability, GER: gastroesophageal reflux.

the group in which an association between reflux and BRUE was found in the MII study as compared to the group where no association was found (10/11 vs. 5/10, p=0.035). None of the patients had repeat hospitalizations or emergency department visits for persistent symptoms.

DISCUSSION

This study demonstrated that only MII-pH monitoring can be used to assess whether BRUE is associated with GER. In addition, better outcomes were found in infants with GER episodes associated with BRUE, indicating the importance of proper diagnosis and treatment. Two possible mechanisms were involved in the causal relationship of BRUE induced by GER: reflex laryngospasm induced by stimulation of the distal esophagus by the refluxate and a chemoreflex in the larynx triggered by the presence of the reflux [20]. The latter is supported by Davies et al. [21], who showed that instillation of water into the pharynx of sleeping human infants elicited a range of chemoreflex responses with predominant receptors for chemoreflex-prolonged apnea located in the pharynx or larynx.

Among infants experiencing BRUE, MII-pH monitoring revealed more than 100 GER episodes in almost half of the patients. Most of these GER episodes were non-acid and weakly acidic, which is consistent with previous studies that showed an association between non-acid GER and acute events (an unexpected change in an infant's breathing, appearance, or

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behavior). If only pH-metry was used, diagnosis would be missed in the majority of children with BRUE induced by GER because none of the non-acid and weakly acid reflux episodes would have been registered. These findings emphasize the importance of MII-pH monitoring in the diagnostic work-up of infants with BRUE induced by GER.

The association between non-acid reflux and BRUE has been previously described. Jarasvaraparn et al. [22] reported pathological GER in 66% of 53 BRUE infants, most of which were non-acid, which was confirmed in the present study. However, they did not find significant differences in the number of reflux episodes between preterm and term infants [22]. Blasco-Alonso et al. [23] reported that of 39 infants presenting with ALTE who underwent 24-hour MII-pH monitoring, 33 were diagnosed with GER. Moreover, they also showed that the number of non-acid reflux episodes was more dominant than that of acid reflux episodes. Furthermore, the latter was confirmed in other studies investigating preterm and term infants with apnea and ALTE, showing that non-acid reflux was more common than acid reflux [24,25]. This is in line with our findings, emphasizing the importance of the combined 24-hour MII-pH monitoring in the diagnostic workup of infants with apnea or BRUE suspected to be induced by GER.

In a study of 23 preterm infants and neonates with apnea, by using 24-hour MII-pH monitoring, Shin et al. [26] found that of the total 998 GER episodes, 407 were acidic, 590 were weakly acidic, and 1 was weakly alkaline, indicating that these 591 episodes would have been missed by pH monitoring alone. Moreover, they showed that of 5 patients with a positive symptom association, 3 were diagnosed by MII-pH, 1 by both MII-pH and conventional pH, and 1 by conventional pH. On the other hand, some studies have shown that the frequency of apneas does not increase following reflux episodes, suggesting that GER does not cause apnea [6,27]. Cresi et al. [8] compared the frequency of GER events between the positive and negative SAP groups. Contrary to our results, they found greater MII-GER frequency in the SAP-positive group than in the negative SAP group. Possible explanations for the discrepancy between the studies could be differences in sample size, diverse clinical characteristics of included infants, and different recording methodologies.

Our study confirmed that in infants, weakly acidic reflux precedes BRUE more frequently than acidic reflux. The importance of weakly acidic reflux as a cause of respiratory phenomena in infants was previously reported by Wenzl et al. [28]. In their study of 22 infants, by using MII-pH monitoring, they found that of all reflux related with breathing abnormalities, 92% were weakly acidic. The explanation for the predominance of weakly acidic reflux might be related to pH buffering due to frequent milk intake in infants. Additionally, the composition and volume of feeding in infants also differed in the study sample.

The appropriate management strategy for infants with BRUE is still controversial due to the limited literature and good prognosis. The latter is in line with the results of our study, since we showed that infants with BRUE have a good prognosis. Moreover, Ari et al. [29] reported a retrospective study of 87 hospitalized infants younger than 1 year who experienced BRUE and concluded that infants hospitalized because of a BRUE seem to have a generally excellent prognosis. It seems that food thickeners treat visible regurgitation/vomiting in infants with GERD; however, their effect on overall GER episodes remains controversial [19]. Medical therapy for GER related to BRUE has not been adequately studied. A systematic review published by van der Pol et al. [30] evaluated the benefits of PPI in reducing GER-related symptoms in infants and found conflicting results. According to that review, omeprazole

has no benefit, while pantoprazole and lanzoprazole are effective in reducing GER-related symptoms in infants.

It is worth mentioning that some evidence suggests an association between acid-suppressive medication in infancy and allergic disease in early childhood [31]; therefore, it is important to confirm and evaluate GER before initiation of medication therapy. This is in line with our findings, since better outcomes were found in those infants in whom a GER-BRUE association was initially observed. This could be explained by the fact that proper treatment led to symptom cessation. However, Duncan et al. [32] showed increased odds of discharge on acid-suppressing medications in infants with BRUE even without GER testing, despite the lack of medication efficacy.

This study has some limitations. First, our study had a small sample size of only 21 infants with BRUE who underwent MII-pH monitoring. Second, we did not combine polysomnography during the MII-pH study, which might determine sleep disorders that can also cause a BRUE. Third, MII-pH tracings were evaluated by only one investigator. Therefore, given some degree of inter-observer variability, it is questionable whether the results reported here would be the same if MII-pH tracings were evaluated by another one. Fourth, we acknowledge the lack of a healthy control group in this study. However, considering the procedure of 24-hour MII-pH monitoring, it is unethical to include infants who are symptom-free. Nevertheless, this study adds important data on the paucity of evidence in infants experiencing BRUE.

In conclusion, our results indicate the superiority of MII-pH monitoring over pH monitoring in the diagnosis of BRUE induced by GER. Further longitudinal studies are needed to investigate the role of esophageal MII-pH monitoring in high-risk BRUE infants.

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