

## Detection of gastroesophageal reflux in children with cerebral palsy using combined multichannel intraluminal impedance-pH procedure

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Received: 18th October 2016, Revised: 10th November 2016, Accepted: 6th January 2017

**SUMMARY:** Çaltepe G, Yüce Ö, Comba A, Özyürek H, Kalaycı AG, Taşdemir HA. Detection of gastroesophageal reflux in children with cerebral palsy using combined multichannel intraluminal impedance-pH procedure. Turk J Pediatr 2016; 58: 524-531.

Gastroesophageal reflux (GER) is a very common condition in children with neurological impairment and this can influence nutritional and respiratory outcomes. The aim of this study was to investigate the presence of GER in children with cerebral palsy (CP) using multiple intraluminal impedance (MII)-pH monitoring. The use of combined MII-pH allows for the detection of both acid and non-acid reflux episodes. A total of 29 CP patients with symptoms suggesting GER, aged 2 to 10 years old, underwent 24-hour combined MII-pH monitoring. There were a total of 3899 reflux episodes, of which 29% were acid, 60% were weakly acid and 11% were alkaline. The number of non-acid reflux episodes was statistically significantly greater ( $p < 0.01$ ). These findings confirm that GER disease is seen frequently in children with cerebral palsy and most of the reflux episodes are not acidic. Non-acid reflux can also influence the morbidity in patients with cerebral palsy. It can be concluded that 70% of the reflux episodes would not have been recognized by pH measurement alone.

**Key words:** cerebral palsy, children, gastroesophageal reflux, multiple intraluminal impedance, non-acid reflux.

Gastroesophageal reflux (GER) is a common problem in neurologically disabled children and when it causes symptoms and/or complications it is known as gastroesophageal reflux disease (GERD). Impairment of the brain may result in significant dysfunction in the gastrointestinal tract<sup>1</sup>. Oro-motor disabilities, swallowing incoordination, abnormal esophageal motility and GER are the most common problems of these children<sup>1-3</sup>. Approximately 75-90% of children with cerebral palsy (CP) have been reported to have GER in different studies<sup>2-4</sup>. Many factors may be involved in the etiopathogenesis of GER in CP patients, including motility disorders, seizures, supine position, and increased intra-abdominal pressure secondary to spasticity and scoliosis. Recurrent episodes of GER can lead to overt

or silent aspiration, vomiting, spillage, food aversion, prolonged feeding times and may result in a significant reduction in nutrient and energy intake<sup>3</sup>.

One of the best methods for the diagnosis of GER is 24-hour esophageal pH monitoring<sup>5</sup>. This method detects reflux in the pH below 4, but GER episodes of weak acidity are not detected with this method. Neonates, infants and neurologically impaired children tend to have weak acid reflux because of the frequent feeding and neutralization of the gastric content following milk or formula<sup>6-8</sup>. Therefore, it is not possible to detect all reflux episodes with pH monitoring. Multichannel intraluminal impedance (MII) is a pH-independent method to investigate the bolus transport in the esophagus, either retrograde

from the stomach or antegrade toward the stomach. The intraluminal catheter also has a pH sensor. Thus, a combined esophageal multichannel intraluminal impedance-pH (MII-pH) technique may detect all GER episodes and classify GER episodes according to their pH value and proximal extension<sup>9-14</sup>.

Early suspicion and the management of GERD has an important impact on the respiratory and nutritional status of children with CP. It is also known that non-acid reflux is as important as acid reflux in these disabled children. Therefore, the evaluation of reflux with combined MII-pH monitoring can allow not only acidic but weak acid and alkaline reflux episodes to be assessed.

The aim of this study was to evaluate GER in children with CP and to evaluate the reflux episodes in terms of acid and non-acid nature.

### Material and Methods

This was a prospective study of children with cerebral palsy aged 2 to 18 years who were referred to the Pediatric Gastroenterology Hepatology and Nutrition clinic for evaluation of GER with symptoms included regurgitation, vomiting, rumination, feeding difficulties and recurrent pulmonary problems. Exclusion criteria were any other chronic cardiac, pulmonary, or metabolic diseases, sepsis, the need for any ventilator support at the time of the study and lack of parental consent. A total of 30 patients who met the criteria were enrolled in the study. The study protocol included a detailed medical history and physical

examination, especially in terms of motor and feeding abilities. The patient motor functions were classified according to the Gross Motor Function Classification System (GMFCS)<sup>15,16</sup>. Anthropometric measurements were taken including body weight and height. As height may not be correctly measured in children with skeletal contractures, scoliosis or an inability to stand, weight measurements were taken into account. Patients were defined as having malnutrition if the weight for age percentile was <10, according to growth charts for children with CP<sup>15</sup>.

All patients underwent 24 hr multichannel intraluminal impedance (MII)-pH monitoring using an ambulatory system (Ohmega, MMS, Enschede, The Netherlands). This system consists of a portable data logger (MMS Investigation and Diagnostic Software®) and a disposable catheter which contains one pH electrode and seven impedance electrodes (Unisensor, Attikon, Switzerland). Before recording, the pH electrode was calibrated in special buffer solutions at pH values of 1 and 7. The catheter was placed transnasally and the pH sensor was situated 2-3 cm above the lower esophageal sphincter (LES), as calculated by the Strobel formula<sup>17</sup> ( $0.252 \times \text{body length [cm]} + 5$ ), and was then confirmed by X-ray. Patients were asked not to use anti-reflux medications for at least five days before the procedure. All the children were admitted to our in-patient unit on the day of the procedure and discharged on the following day. During the monitoring period, patients were permitted to continue

**Table I.** Characteristics of the Patients with Cerebral Palsy

Patients	n=29
Age, years, mean±SD (median, range)	4.0±2.3 years (3.5; 2-10 years)
Male/Female ratio (%)	13/16 (44.8/55.2)
Types of cerebral palsy, n (%)	
Spastic	15 (51.7%)
Generalized hypotonic	10 (34.5%)
Mixed	4 (13.8%)
Gross motor function classification (GMFC)	
Class IV	1 (3.5%)
Class V	28 (96.5%)
Tube feeding	7 (%)
Weight for age percentile*	
< 10 p	17 (58.6%)
10-50 p	11 (37.9%)
> 50 p	1 (3.5%)

\*According the growth charts for children with CP

Table II. Symptoms and Presenting Features of the Patients\*

Symptoms	Number of patients (n=29)	%
Gastrointestinal	19	65.5
Feeding difficulties	19	65.5
Constipation	15	51.7
Vomiting	12	41.4
Inability to swallow	7	24.1
Rumination	4	13.8
Hematemesis	3	10.3
Pulmonary	17	58.6
Chronic cough	17	58.6
Wheezing	13	44.8
Recurrent pneumonia	10	34.5

\*Patients were presented with more than one symptoms.

daily activities and oral or enteral intake of anything except acidic foods. Caregivers were asked to press the labeled buttons and complete a diary recording at the same time for the meals and body position. The MII-pH data were analyzed using MMS software and were manually reviewed by the same investigator (G.Ç.). Written informed consent was obtained from the parents or legal guardians of all the study participants. The study was approved by the Ethics Committee of Ondokuz Mayıs University Hospital.

#### Definitions<sup>5,10</sup>

pH reflux index (RI); percentage of time with esophageal pH<4.

Reflux index > 4% was accepted as a positive test result for pH monitoring

MII reflux event (MIIe); decrease in impedance to <50% of the baseline value in at least two channels with upward direction.

Acidic MIIe; episode detected by MII with pH<4.

Weakly acidic MIIe; episode detected by MII with pH of 4 - 7.

Alkaline MIIe; episode detected by MII with pH>7

A total of >50 reflux events in 24 hours was accepted as a positive test result for MII monitoring.

#### Statistical analysis

Statistical analysis was performed using SPSS version 20.0. Data were expressed as mean± standard deviation (SD), as median (min-max) and as frequency (n) and percentage (%). The Mann-Whitney U test was used to compare variables between two independent groups and the non-parametric Wilcoxon Signed Ranks test was applied to two dependent groups. A value of p< 0.05 was considered statistically significant.

#### Results

A total of 30 children were enrolled in the study. One patient was excluded due to technical problems in MII-pH tracings. Sufficient data was obtained from 29 patients with a mean age of 4.0±2.3 years (median: 3.5 years; range 2-10 years). The patients comprised 16 (55.2%) females and 13 (44.8%) males. There were 15 (51.7%) spastic, 10 (34.5%) generalized hypotonic and 4 (13.8%) mixed type of CP patients. All the patients had severe neurological deficiency of class IV-V according to the CMFCS. On presentation, 7 patients were already fed by tube (Table I).

According to the growth charts for children with CP, the bodyweight of 17 (58.6%) of the included patients were <10<sup>th</sup> percentile, 4 of whom were tube-fed patients. Nearly all (96.5%) the patients were < 50<sup>th</sup> percentile.

The patients presented with a wide range of symptoms, mainly classified as gastrointestinal

**Table III.** Mean Values of the pH Measurements

Parameters	Mean $\pm$ SD (median; range)
Reflux index (RI) (%)	16.0 $\pm$ 15.2 (10; 2.3-48.3)
Number of reflux events	62.4 $\pm$ 64.2 (42; 3-324)
Number of reflux events lasting > 5 min	10.2 $\pm$ 13.3 (5; 1-47)
Longest reflux event (min)	28.8 $\pm$ 20.7 (25.9; 5.7-68.8)
Lower pH ever reaching	1.1 $\pm$ 0.7 (1.1; 0-2.7)

**Table IV.** Comparison of Multichannel Intraluminal Impedance and pH Monitoring

	pH monitoring positive	pH monitoring negative	Total
MII monitoring positive	20	5	25
MII monitoring negative	2	2	4
Total	22	7	29

Kappa = 0.228 (p=0.193, 95%CI: 0.000-0.630)

and pulmonary symptoms (Table II). A total of 19 patients presented with mainly gastrointestinal symptoms, and 17 with pulmonary symptoms (7 in both groups had both kinds of symptoms).

A total of 674.6 hours (mean 23.3 h/patient, range 19.2-25.4 hours) of tracings were analyzed during the MII-pH monitoring. In the analysis of the pH recordings, 1810 episodes were identified as reflux events. The mean number of reflux events was 62.4 $\pm$ 64.2 and the mean RI was 16.0% $\pm$ 15.2%. Twenty two out of 29 patients (75.8%) had positive test results according to reflux index. The mean values of the pH measurements are shown in Table III.

There were a total of 3899 reflux episodes during the study according to the MII-pH monitoring, 25 patients (86.2%) had positive test results. The comparisons of MII and pH monitoring showed that pH monitoring alone missed 5 patients (Table IV).

In the examination of pH values of MII-pH monitoring, 1128 (29.0%) were classified as acid, 2333 (60.0%) as weakly acid and 426 (10.9%) as alkaline. 682 out of the 1810 refluxes (37.6%) detected by pH monitoring were not detected as acidic reflux with MII-pH. This may be due to the shortness of the events or the inability of the reflux to reach the upper channel. The mean numbers of acidic and weakly acidic MII events (MIIe) were 38.9 and 80.4 respectively (Table V). The number

of weakly acidic reflux events were determined as 2-fold more than acidic reflux and this was statistically significant (p<0.010). When evaluation was made in terms of proximal extension, 1879 of 3899 MIIe (48.2%) were found to reach the most proximal channel Z1.

In respect of nutritional status, there were no significant differences between patients with and without malnutrition in terms of MII-pH parameters (Table VI). When patients with and without respiratory symptoms were compared, no significant differences were determined in MII-pH parameters (Table VII). Patients were grouped as spastic (n=15), generalized hypotonic (n=10) and mixed (n=4) according to the type of CP. There were no significant differences between these groups in terms of MII-pH parameters (Data is not shown).

## Discussion

Gastrointestinal problems are well known to be a frequent occurrence in children with CP. Studies have shown that feeding difficulties, chronic pulmonary aspiration, constipation, malnutrition and GER are the major problems in children with CP<sup>1,2,18,19</sup>. Many studies have indicated that patients with CP, particularly in its severe form, are at high risk of developing GERD<sup>2,20,21</sup>, which is probably because of the generalized dysmotility and the altered mechanism of the lower esophageal sphincter. A high frequency of GER, up to 90%, depending on the diagnostic method, has been reported in neurologically impaired children in different

Table V. Mean Values of the MII-pH Measurements.

Parameters	Mean ± SD (median; range)
Total number of MIIe	134.5±122.9 (109; 20-561)
Number of acidic MIIe	38.9 ± 61.7 (17; 1-311)*
Number of weakly acidic MIIe	80.4 ± 72.8 (53; 9-303)*
Number of alkaline MIIe	14.7 ± 46.3 (1; 0-242)
Total number of MIIe reaching Z1 channel	79.8±77.0 (42; 2-289)
Acidic MIIe reaching Z1 channel	26.1±38.4 (13; 1-151)
Weakly acidic MIIe reaching Z1 channel	38.4±45.8 (15; 1-162)
Alkaline MIIe reaching Z1 channel	15.4±34.6 (15; 1-119)

\*p&lt;0.010

MIIe; Multichannel Intraluminal Impedance event

studies<sup>2,18,22</sup>. Many different methods such as nuclear scintigraphy, barium contrast graphs, endoscopy and biopsy, esophageal pH-metry and impedance have been used to diagnose GER. There are advantages and disadvantages of each method, and the facilities and experience of the center are also important when selecting the test to be used. Esophageal pH-monitoring is one of the most convenient methods but it only recognizes acidic episodes of reflux<sup>12,13,23,24</sup>. A significant proportion of reflux episodes are known to be non-acidic, especially in infants<sup>23-27</sup>. As emphasized in the most recent guidelines, combined multiple intraluminal impedance and pH monitoring (MII-pH) is the most reliable method to evaluate GER<sup>5,10</sup>.

MII-pH recognizes all reflux episodes including non-acidic ones. This is also important in neurologically impaired children who are frequently fed liquid meals<sup>8,22</sup>.

Multiple intraluminal impedance technique is based on the ionic concentrations of the luminal contents<sup>6,10</sup>. Bolus with no ionic contents, such as gas (air), results in a rise in impedance but relatively high ionic contents such as refluxate results in a drop in impedance. A bolus-liquid reflux is defined as a retrograde drop in impedance of at least 50% of the baseline level. The use of MII technique allows the analysis of movement direction and proximal extent of the bolus. When a pH sensor is added to the MII catheter, it can also discriminate both

Table VI. MII-pH Comparison Between Patients with and Without Malnutrition

	Group I (n=17)	Group II (n=12)	P
Age (year)	4.5±2.7 (4; 2-10)	4.2±3.0 (3.2; 2-10)	0.738
Number of MIIe	153.1±154.9 (111; 60-561)	170.1±139.1 (109; 20-388)	0.121
Acidic	34.8±27.8 (21; 1-89)	81.3±114.5 (44; 11-311)	0.097
Weakly acidic	90.2±84.1 (62; 36-303)	78.4±70.3 (62; 9-209)	0.535
Alkaline	28.5±80.0 (2; 0-242)	10.2±10.5 (8; 0-23)	0.053
MIIe reaching Z1 channel	107.1±84.2 (70; 2-277)	89.1±101.0 (50; 14-289)	0.236
Acidic	26.1±38.6 (123; 1-126)	41.5±54.4 (22; 11-151)	0.687
Weakly acidic	57.0±59.8 (42; 6-162)	45.6±48.4 (32; 1-136)	0.182
Alkaline	24.1±43.3 (1; 1-119)	2.2±2.3 (1; 1-7)	0.112
Reflux index (RI) (%)	16.7±14.5 (12; 2-48)	13.6±16.4 (6; 2-45)	0.740
Reflux events lasting >5 min	9.0±9.3 (6; 1-30)	11.3±17.9 (3; 1-47)	0.982
Longest reflux event (min)	38.6±22.1 (39; 5-69)	19.0±14.5 (13; 7-45)	0.150

Data is expressed as mean±SD (median; range)

Group I: Weight for age percentile < 10 P; Group II: Weight for age percentile ≥ 10 P, according to growth charts for CP patients<sup>15</sup>

MIIe; Multichannel Intraluminal Impedance event

**Table VII.** MII-pH Comparison Between Patients With and Without Pulmonary Symptoms

	Patients with pulmonary symptoms (n=17)	Patients without pulmonary symptoms (n=12)	P
Age (year)	3.4±2.0 (2.5; 1-9)	5.2±3.0 (5.5; 2-10)	0.080
Number of MIIe	109.8±83.3 (110; 21-291)	169.4±161.5 (103; 20-561)	0.647
Acidic	33.9±39.6 (21; 1-151)	45.9±85.6 (16; 1-311)	0.948
Weakly acidic	71.2±54.9 (53; 10-209)	93.4±93.8 (54; 9-303)	1.000
Alkaline	3.8±7.7 (0; 0-23)	30.0±70.2 (5; 0-242)	0.073
MIIE reaching Z1 channel	44.8±37.8 (41; 2-126)	105.6±104.3 (72; 7-289)	0.162
Acidic	17.3±18.0 (13; 1-69)	38.9±53.7 (16; 4-151)	0.483
Weakly acidic	24.8±22.0 (14; 1-69)	58.0±63.3 (25; 3-162)	0.342
Alkaline	12.0±26.6 (3.5; 1-78)	19.2±44.0 (2; 1-119)	0.955
Reflux index (RI) (%)	14.30±12.3 (11; 2-48)	12.4±14.2 (6; 2-45)	0.347

acid and non-acid reflux<sup>6,10,11</sup>. In the current study, a total of 3899 reflux events were detected by MII-pH, of which only 29% were acidic. Impedance probes identified more reflux episodes than the pH probes (3899 vs 1810). Thus, the mean number of weakly acidic reflux episodes were determined at double the rate of the mean number of acidic reflux episodes, which was statistically significant ( $p < 0.01$ ). In a recent study, Liu et al.<sup>26</sup> showed that MII-pH monitoring detected a 3-fold increase in non-acid reflux episodes in comparison with acid reflux episodes. The impact of non-acid reflux is very important in a study population such as the one in the current study. Non-acid reflux is known to be mostly seen in infants because of the frequent feeding and the buffer effect of the milk. There may be a similar effect in neurologically disabled children, because they are fed with liquid formulas and need much more time to finish each meal. Therefore both acid and non-acid reflux events may precede symptoms in children with CP.

The results of the current study indicate that malnutrition is a very common condition in children with CP, which is in agreement with previous studies<sup>1,2</sup>. It is thought to occur not because of increased energy expenditure, but because of inadequate energy intake<sup>18,28</sup>. Conditions such as oro-motor dysfunction, chewing and swallowing difficulties and GER cause prolonged mealtimes and inadequate nutrition. Severely neurologically handicapped children in particular are at great risk of developing malnutrition<sup>1,28-30</sup>. In a recent study, patients with CP had significantly lower

anthropometric measurements than a control group and the difference was particularly evident in patients with a higher grade of motor disability<sup>20</sup>. In the current study, all the patients had high degree neurological disabilities of grade IV-V according to the GMFC. In 58.6% of the patients, bodyweight was  $< 10^{\text{th}}$  percentile according to the CP special growth charts. This high percentage of malnutrition was not a surprise because they were severely disabled patients, being fed with semi-liquid or puree type foods and almost one quarter were already on tube feeding. To evaluate if there was any impact of GER on malnutrition, children with and without malnutrition were compared. The mean values of the MII-pH monitoring parameters did not reveal any significant difference, including the number of acid and non-acid reflux episodes. Even though no significant difference was determined in the effect of acid and non-acid reflux on nutrition, it was observed that reflux episodes reaching the proximal channel constituted almost half of the total reflux episodes. It may be assumed that high GER reaching the proximal channel is particularly meaningful in children with pulmonary symptoms, suggesting the possibility of micro aspiration of gastric contents into the bronchial tree<sup>31</sup>. The pH value of reflux episodes is important especially in infants<sup>9</sup>. In previous studies, a stronger association has been found between non-acid reflux episodes and respiratory symptoms in children with chronic respiratory disease<sup>32,33</sup>. In a recent study, the authors observed a higher prevalence of weakly acid reflux in infancy

in otherwise healthy children with a chronic unexplained cough<sup>34</sup>. To make an evaluation from this perspective, children with and without respiratory symptoms were compared but no significant difference was determined in terms of acid, non-acid reflux and proximal extension of the reflux.

In conclusion, GER is frequently seen in children with CP and it causes gastrointestinal and pulmonary morbidity. The great majority of reflux events are non-acidic. The results of this study confirms that non-acid reflux episodes are seen much more than acid reflux in children with CP and MII-pH monitoring is more effective than pH alone studies in detecting all reflux events.

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