

NON ACID GASTROESOPHAGEAL REFLUX EPISODES DECREASE WITH AGE AS DETERMINED BY MULTICHANNEL INTRALUMINAL IMPEDANCE-PH MONITORING IN SYMPTOMATIC CHILDREN.

DISMINUCION CON LA EDAD DE LOS EPISODIOS DE REFLUJO GASTROESOFAGICO NO ACIDO DETERMINADOS POR IMPEDANCIA INTRALUMINAL MULTICANAL Y PHMETRIA EN NIÑOS SINTOMATICOS

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Resumen

Objetivos: Determinar si los cambios de reflujo gastroesofágico (RGE) relacionados a la edad en pacientes pediátricos sintomáticos, medidos por Impedanciometría Intraluminal Multicanal (IIM).y pH-metría de 24 horas (pH), se deben a reflujo ácido, no ácido o ambos.

Métodos: Se revisaron y analizaron usando la prueba de Mann-Whitney U trazados simultáneos de IIM-pH de 243 niños que presentaron con síntomas digestivos o respiratorios atribuibles a RGE.

Results: El número de episodios registrados de RGE fue semejante en niños con síntomas predominantemente gastrointestinales que en aquellos con síntomas respiratorios. Se observó un número significativamente más grande de RGE por pH e IIM en niños debajo de los 22.8 meses de edad comparado con los mayores de esa edad (media 159 vs. 110.5, $p = 0.002$). No hubo un cambio significativo con la edad en los parámetros relacionados a reflujo ácido (RA). Los cambios observados se debieron a una disminución significativa del reflujo no ácido en todos los parámetros estudiados, independientemente de los síntomas de presentación.

Conclusiones: La disminución en los parámetros de RGE que se observan con la edad después de una media de 22.8 meses de edad se hace a expensas del reflujo no ácido. Esto puede tener un impacto en la elección y resultado de las modalidades terapéuticas en niños mayores versus los más pequeños.

Palabras clave: reflujo gastroesofágico, impedancia intraluminal multicanal, niños, reflujo no ácido, pHmetría

Summary

Objectives: To determine whether changes related to age in gastroesophageal reflux (GER) in infants and children are due to acid, non acid reflux or both, as determined by 24 hr pH probe (pH) and Multichannel Intraluminal Impedance (MII).

Methods: Tracings of simultaneous pH-MII from 243 infants and children who presented with either digestive or respiratory symptoms attributable to GER were reviewed and analyzed using Mann-Whitney U test.

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Results: The number of GER episodes recorded was similar among children with predominantly gastrointestinal and those with respiratory symptoms. A significantly higher total number of GER episodes was observed by pH probe and MII in children under 22.8 mos of age compared with those who were older (median 159 vs. 110.5, $p = 0.002$). There was no significant change with age of acid reflux (AR) parameters. The changes observed were due to the significant decrease of non AR for all parameters measured, regardless of the presenting symptom.

Conclusions: The decrease in GER parameters that is observed after a mean of 22.8 mos. of age is at the expense of non AR. This finding may have an impact on the choice and results of therapeutic modalities in children versus that in infants.

Key words: gastroesophageal reflux; multichannel intraluminal impedance; non acid reflux; pH probe

INTRODUCTION

Many young infants experience gastroesophageal reflux (GER) which progressively improves until it disappears the latest at one and one half years of age (1,2) The multichannel intraluminal impedance (MII) records acid and non acid reflux events (3,4). The system records changes in resistance (in Ohms) as a result of alternating electrical current that occurs whenever a bolus passes by a pair of metallic electrodes mounted on a catheter. Combined with pH (multichannel intraluminal impedance and pH; MII-pH) it permits detection of both acid and non-acid gastroesophageal reflux. MII detects bolus refluxate independent of the pH composition of the refluxate, whereas the pH sensor cannot differentiate reflux from a swallow (5,6). The aim of this study was to determine whether changes related to age in GER in infants and children presenting with either gastrointestinal or pulmonary symptoms are due to acid, non acid reflux or both, as determined by pH-MII.

METHODS

The records of 243 infants and children referred by pneumonologists, otorrhinolaringologists and pediatricians to the Pediatric Gastroenterology Unit of the Hospital Italiano in Buenos Aires, Argentina between January 2005 and December 2006 for the evaluation of their GER symptoms were reviewed. Patients with cardiac disease, congenital anomalies, feeding disorders, mental retardation and cerebral palsy were excluded. Patients receiving gastric acid suppressing drugs had their medication discontinued 2 wks prior to the study. GER symptoms were divided into: 1) Digestive,

which were subclassified as being (a) epigastric (pain, upper abdominal pain, and/or heartburn), (b) emesis, (c) irritability, crying, d) non mechanical feeding difficulties and, 2) Respiratory: (a) low respiratory symptoms (recurrent pneumonia, wheezing, obstructive bronchitis and bronchospasm), (b) high respiratory symptoms (recurrent cough, hoarseness and throat clearing, (c) suffocation (choking, acute life threatening episode, and apneas). Patients with digestive symptoms were referred to us because of persistence or recurrence of symptoms despite adequate initial management by their primary physicians. These patients were considered to have GER if the clinical history was supportive of that diagnosis. All had an upper gastrointestinal radiological study to rule out a duodenal anatomical malformation or malrotation. Patients with respiratory symptoms were referred to us because of failure to respond to management of their pulmonary symptoms as implemented by their primary physicians or pediatric pulmonologists. Patients presenting with more than one symptom were classified according to the main symptom or primary reason for consultation.

Procedure

Patients were admitted to the hospital for a 24 hr continuous study evaluating the preprandial, postprandial and sleep periods using pH-MII testing. The pH sensor is located within the distal channel. The length of the catheter was chosen according to the patient's age. Correct catheter placement was confirmed by a chest radiograph. Parents and patients were instructed to maintain as normal a daily routine and diet as possible. Before the initiation of the study, caretakers were

asked to identify three symptoms of concern for their child. Three buttons in the recording machine were labeled with these symptoms and caretakers were asked to press the appropriate one whenever their child presented that symptom during the study. pH-MII tracings were evaluated using BioVIEW analysis software (Sandhill Scientific, Inc. Highlands Ranch, CO, USA), and each study was manually reviewed by one of the investigators.

pH-MII analysis

Using the pH-MII technique, we identified liquid refluxate and whether reflux was acid or non acid. An impedance detected reflux event was defined as a retrograde bolus movement across at least two channels that caused the impedance to drop at least 50% from baseline (7). To label the impedance detected refluxate as acid, the pH had to fall below 4.0 any time the bolus was physically present in the distal channel. Symptoms such as choking while not being fed, cough, intense crying and vomiting were considered related to a reflux event if it occurred within a 5 min window (5 min before a reflux event, the time that was accepted at the time when these studies were performed, or immediately after) (8,9). If a symptom recurred within 1 minute, this symptom record was considered a duplicate of the preceding symptom and was removed from the analysis. To evaluate the detection of a reflux event in relation to the time from the last meal, reflux records that occurred before the first meal were not included in the analysis. The following parameters were considered as normal when calculating pH score (percent of the time that esophageal pH was below 4): number of episodes with pH below 4, episodes longer than 5 min: <5.8, total reflux time <5.1, most prolonged episode: <22.4, total number of reflux episodes: <27.0 (10,11). The bolus exposure time value used was that reported by the Sandhill autoscan.

DATA ANALYSIS

Patients were grouped according to their primary presenting symptoms into a digestive (regurgitation, vomiting, epigastric pain, heartburn) or a respiratory (recurrent cough, laryngitis, pneumonia, bronchospasm, asthma) group. Patients were divided in two age groups according the median age.

STATISTICAL ANALYSIS

The normality of data was assessed using the Kolmogorov-Smirnov and Lilliefors tests. For the purpose of descriptive analysis, mean or median (first and third quartiles) were applied in the case of normal or non-parametric distributions. The Mann-Whitney U and Differences at 0.05 level were considered significant. For all statistical analyses, Statistica (Version 6.0, Statsoft, Tulsa, OK) was used.

RESULTS

Two hundred and forty three infants and children were included, (144 males; mean [+ SD] age was 3.9 + 4.5 yrs [range 0.04 – 18.0 yrs]). Two patients had uninterpretable data in both tests and were excluded from analysis, therefore data from 241 are presented. In the few cases where recordings experienced technical problems, those studies were also excluded from the analyses. The sensitivity (SSI) and probability index (SAP) were not analyzed. Actual number of studies analyzed for each parameter is listed in the Tables.

Age

Median and inter quartile range for the whole population was 1.91 [0.41 -7.0 yrs. and this was adopted as a cut-off value.

pH probe

Median (inter quartile range) of the total number of GER episodes among 241 patients was 117 (16.4 -166) with a range from 0 to 243. No significant differences were found between the pH scores of patients with digestive symptoms (median, 1st - 3rd quartile) (7.15, 3.3 – 18.1) and those with respiratory symptoms (5.95, 2.6 – 14.8), ($p = 0.096$) or between those with high (6.2, 2.6 – 14.6) or low respiratory symptoms (5.8, 2.2 – 12.8), ($p = 0.997$) (Table 1). Also, no significant differences were found in the total number of GER episodes of those with digestive symptoms (124.5, 26 – 173) compared to those with high or low respiratory symptoms (117, 15.2 – 154), ($p = 0.113$).

However, when data were analyzed according to age, a significantly higher total number of GER episodes were observed in children under the age of 1.91 yr (22.8 mos) compared to those who were older (median 159 vs. 110.5, $p=0.002$). Fifty one percent of the patients ($n=124$) were 22.8

mos of age or younger. However, there was no statistically significant difference in the pH score between the younger and older children.

MII

Bolus clearance was significantly faster in the younger group (median 14 seconds, range 11-16) vs. 16 seconds (14-20) ($p = 0.001$) (Mann-Whitney U Test). The percentage of time acid exposure of the esophagus failed to reach significant difference between the younger and older children (median 0.8 and 1, respectively; $p = 0.057$). Finally, there was no significant difference between the younger and older age groups with respect to the median number of GER episodes that reached channels 1 and 2: 65.4 vs. 118 ($p = 0.306$). Median (inter quartile range) total number of GER episodes detected by MII among 243 patients was 40 (26 -58). Of these, 20.5 (10 -34) were acid and 16 (9 -29) non acid. Of these, a mean of 29.7(+ 67.2) (IC 95% 21 – 38) were acid and 20.6 (+ 17) (IC 95% 18.4 – 22.7) non acid. As seen with the pH probe, children older than 1.91 yr (22.8 mos) had a significantly lower number of GER episodes than those who were younger for both clinical presentations, digestive and high and low respiratory symptoms (Table 1). When GER episodes were separated into acid and non acid, significant differences related to the 22.8 mos cut-off age were seen in the total number of non acid GER episodes for children with either digestive, total respiratory or high/low respiratory symptoms but no significant changes for acid episodes (Table 2).

Table 1: Comparison of several GER parameters determined by 24 h pH probe and Multichannel Intraluminal Impedance (MII) studies for patients presenting with either digestive or respiratory symptoms according to their age.

Parameter	n	Age ≤ 1.91 y	n	Age > 1.91 y
pH Score	124	7.1 (2.8 – 18.5) ^a	119	6.4 (2.6 – 14.8) ^a
Total number of episodes by pH meter	121	159 (15 – 191) ^b	120	110.5 (17.6 – 138.5) ^b
Digestive episodes by MII	49	163 (21–191) ^c	35	115 (39-146) ^c
High & low respiratory by MII	31	178 (22-199) ^d	83	111 (14-138) ^d

n = number of subjects studied
Values expressed as Medians (1st and 3rd quartile)
Mann-Whitney U test.

a, c: $p > 0.05$
b: $p = 0.001$
d: $p = 0.002$

Comparison of pH probe and MII

Comparing the median total number of GER episodes detected by the two techniques, the pH probe consistently showed a higher number of GER episodes for all patients regardless of their

presenting symptoms or age (Table 1). The only concordance between pH probe and MII among the factors analyzed was the finding of the difference in the number of GER episodes above or below the age of 22.8 mos.

Table 2: Total number of acid and non acid GER episodes from 24 Hr Multichannel Intraluminal Impedance studies for patients presenting with either digestive or respiratory symptoms according to age.

GER episodes	ACID				NON ACID			
	n	Age ≤ 1.91 yr	n	Age > 1.91 yr	n	Age ≤ 1.91 yr	n	Age > 1.91 yr
Total	120	19.5 (8-32) ^a	122	21 (10-37) ^a	121	21 (14-38) ^b	121	11 (7-19) ^b
Digestive	49	26 (13-40) ^c	35	23 (14-46) ^c	49	19 (14-36) ^d	34	12 (6-19) ^d
Total Respiratory	31	25 (8-37) ^e	85	18 (9-31) ^e	31	18 (13-36) ^f	83	10 (7-19) ^f
High respiratory	4	27.5 (16-33) ^g	25	22 (10-45) ^g	4	23.5 (9.5-38) ^h	25	9 (7-17) ^h
Low respiratory	27	25 (8-37) ⁱ	58	18 (8-30) ⁱ	27	18 (13-36) ^j	58	11 (6-21) ^j

n = number of subjects studied
Values expressed as medians (1st and 3rd quartile).
Mann-Whitney U test.

a, c, e, g, i: $p > 0.05$
b, d: $p < 0.001$
f, h, j: $p < 0.05$

DISCUSSION

Recently published guidelines for pediatric gastroesophageal reflux indicate that combined pH and MII monitoring is superior to pH monitoring alone for evaluation of the temporal relation between symptoms and GER (10). In our study we used a standard protocol for the interpretation of pH recordings to measure acid reflux (11,12). The MII test detects the bolus of refluxate and is therefore independent of pH, providing a more accurate determination of reflux of any sort into the esophagus (13).

We were able to identify a difference in the median number of reflux episodes among symptomatic patients according to their age. In that regard, we found that for several of the parameters measured, 22.8 mos was the age after which the median number of events recorded decreased significantly. As we stated, that age was the median of the group studied and we used that arbitrarily, as it is close to 18 mos, when children are found, at least clinically, to outgrow their reflux symptoms (1,2). A more recent study indicated that 88% of 210 infants with GER who had completed a 24 mos follow-up period had improved at the age of 12 mos and only 1 patient later turned out to have GER disease (14). Although we do not present follow up studies of our study patients, it would seem that, as a group, older patients who are symptomatic have lower number of GER episodes than

younger ones

We confirmed several findings of previous studies. In this large number of patients studied, we have also documented a greater number of GER episodes of pH only compared to those of bolus GER (5,15). Studies in adults and children have recognized the significant role of non acid reflux, previously undetectable when the pH probe technique was used by itself (16). Non acid reflux has been identified as being more prevalent than acid reflux. Our study not only corroborated that predominance but allowed us to identify a decrease in the median number of these episodes among symptomatic children older than 22.8 mos. Such age differences were significant for total number of GER episodes, for patients with predominantly digestive symptoms and for those with predominantly respiratory symptoms, both for total number of episodes and for those who presented high and low respiratory symptoms. Interestingly, there was no significant decrease with age on acid reflux. Our study did not address, however, the fact that greater day to day variation has been found with respect to non acid than to acid reflux (17). Our data indicate that the number of non acid reflux episodes is more dependent on age than acid episodes, and that supports the idea that MII may be useful for the study of the physiopathology of GER. Although statistically we also found a significantly shorter clearance time among the younger group, it may be that clinically that difference is not relevant.

One of the findings in this study is that there was no significant decrease of acid GER with age. This is in contrast with the current gold standard, the pH-metry that has a higher cut-off value in infants than in children, as defined by Vandenas (18). There are several explanations to this discrepancy. One explanation could be that the pH probe is unable to differentiate between variations related to acidic feeding (yoghurt-fruit juices-soda beverages) so common in infant feedings from true pH drops related to acid reflux. Additionally, being ours a retrospective study, there could have been a bias to studying children who were very symptomatic and thus a decrease in pH scores was not observed.

A limitation of this study is that we did not take into consideration mixed reflux episodes, which are a combination of air and liquid refluxate that

have a significant role in GER, nor the so called acid vapor gaseous refluxes. The reason for this is that at the time we performed the studies, investigators were not aware of the relevance of these episodes.

Guidelines by the North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN/ESPGHAN, respectively) recommend the use of MII to study patients suspected of having GER who are on acid suppressing medication while the pH probe should be used in those not receiving those medications (10). Recent data indicates that MII-pH doubles the probability of documenting an association between symptoms and reflux compared with pH monitoring alone (6,18). In addition, in young infants, symptoms are more frequently associated with weakly AR than with AR a parameter that we did not record in our study (19).

In conclusion, after the median age of 22.8 mo. we observed a decrease of non acid reflux. This finding may have an impact on the choice of therapeutic modalities in children versus infants as well as better understanding their response to available medications.

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