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Original Research Article

Gastroesophageal Reflux Disease in Premature and Term Infants Examined Using Intraluminal Impedance and pH Monitoring

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Abstract

Preterm infants represent a population at high risk for gastroesophageal reflux disease (GERD) development. To measure the frequency of GERD in former premature infants and to compare it with that of a general population of pediatric patients with signs and symptoms suggestive of GERD, in order to find an association between premature birth and risk of GERD. The study group consisted of 19 former premature patients who were referred to the physician and hospitalized for symptoms suggestive of GERD. The control group consisted of 24 patients with no history of prematurity and suspected of GERD, selected according to the order of hospital admission. All patients underwent a 24-hour multichannel intraluminal impedance combined with pH monitoring. Pathologic GER was more frequent in the study group (63,16%) than in the control group (62,5%). Prematurity didn't increase the risk of GERD development (OR 1,02; CI 95% 0,2-3,5). The comparison between children categories revealed a slightly higher GERD frequency in former premature children (63,64%) compared to control children (61,54%). Also in this case, there was not a significant association between preterm birth and GERD development in children (OR 1,03; CI 95% 0,28-3,37). GERD was more common in control infants (63,6%) than in former premature infants (62,5%). There was a negative association between prematurity and GERD in this category of patients (OR 0,9; CI 95% 0,22-4,25). Our findings do not demonstrate a significant association between prematurity and GERD development during infancy and childhood. The topic warrants further investigation by future research.

Key words: Gastroesofageal reflux, Prematurity, Intraluminal impedance, pH monitoring

INTRODUCTION

Gastroesophageal reflux disease (GERD), defined by the presence of troublesome symptoms caused by gastroesophageal reflux (GER), is one of the most common gastrointestinal disorders in children (Sherman et al. 2009; Lightdale and Gremse 2013). It represents a possible chronic condition with a long-term evolution associated with the development of potentially serious complications (Lightdale and Gremse, 2013; Vandenplas et al., 2005).

Complications like esophageal strictures, Barrett's esophagus and esophageal adenocarcinoma, widely described in adults, are rare in children and are more frequently seen in a few categories of "at risk" patients (Lightdale and Gremse, 2013). Pediatric patients with

neurologic impairment, history of esophageal atresia, hiatal hernia, chronic lung disease and premature infants are considered at high risk for developing chronic and severe GERD and associated complications (Lightdale and Gremse 2013; Vandenplas et al. 2009). Among the mentioned predisposing factors, this study focuses on the relationship between GERD and prematurity, evaluating the effect that a premature birth may have on GERD development during infancy and childhood.

It is established that GERD is a very common disorder in preterm infants (Corvaglia, et al., 2013; Kültürsay, 2012), representing a frequent cause of prolongation of hospital stay in this category of patients (Mendes et al., 2008). Approximately 25% of premature infants are prescribed with anti-reflux medications at the moment of discharge from the neonatal intensive care unit (Malcolm et al. 2008).

The increased risk of pathologic and non-pathologic reflux in preterm babies may be explained by immaturity of anatomic and physiologic mechanisms that normally limit reflux (Kültürsay 2012; Schurr & Findlater 2012; Henry 2004; Omari et al. 1995). The prolonged use of assisted nutrition and the presence of comorbidities frequently associated with prematurity also contribute in favoring the onset of GERD (Vandenplas et al. 2005).

However, what is still less clear is whether the patients who were born prematurely are at higher risk of GERD development when they reach corrected postnatal ages as well, during infancy and childhood. A more extensive knowledge of the natural history of GERD in premature infants following the neonatal period would lead to a further improvement in the management of pediatric patients with this disease.

Different studies have tried to evaluate the association between prematurity and the onset of GERD and its complications later in life and have resulted in variable findings.

Because of this, further research is necessary to strengthen the hypothesis that prematurity predisposes the pediatric patient to GERD development in infancy and childhood, and also later in life; knowing that serious GERD complications like Barrett's esophagus and esophageal adenocarcinoma may be promoted by long-term exposure of the esophageal mucosa to acid reflux (Sherman et al. 2009). The determination of a specific and definite correlation between prematurity and GERD would allow for a better follow-up and management of former premature patients.

Therefore, starting from the hypothesis that preterm birth is followed by an increased risk of GERD development during infancy and childhood, this study has the purpose to provide additional data on the association between prematurity and GERD by examining the frequency of the disease in former premature infants compared to a general population of pediatric patients with no history of prematurity. The study wants to determine if the prevalence of pathologic reflux is higher in patients delivered prematurely than in those who were born at term and if GERD with prematurity as risk factor has the same frequency in different pediatric age groups (infants, children). To test the hypothesis, pediatric patients of different ages with a symptomatology suggestive of GERD were selected and divided into a study group and a control group according to the presence of a history of prematurity. A 24-hour multichannel intraluminal impedance combined with pH monitoring (MII-pH monitoring) was performed in all patients in order to obtain an objective diagnosis and to characterize the reflux.

MATERIALS AND METHODS

This was a retrospective cohort study that was conducted at Marie Curie Emergency Children Hospital, in Bucharest, Romania. The data used for the purpose of the study were collected from patients' files inserted in the computer system of the hospital. The system provided information on patients' medical history and physical examination, and on MII-pH monitoring procedure and results.

Patients

The study group included 19 former premature pediatric patients who were referrewith October 2012. The age of the patients in the study population was less than 10 years old, ranging between 6 months and 9 years old.

Prematurity was defined as birth occurring before the 37^{th} week of gestation and as weight at birth below 2500 grams. The birth characteristics of each patient, including gestational age and weight at birth, were assessed. According to their weight at birth, children were classified into 4 groups indicating their degree of prematurity: 9 preterm infants of 1^{st} degree (weight at birth 2499g-2000g), 4 of 2^{nd} degree (weight at birth 1999g-1500g), 3 of 3^{rd} degree (weight at birth 1499g-1000g) and 3 of 4^{th} degree (weight at birth below 1000g).

Former premature patients with previous surgical interventions (repaired esophageal atresia, anti-reflux surgery), neurologic impairment and collagen diseases were excluded from the study.

The control group consisted of 24 patients, who had no history of prematurity, hospitalized for symptoms suggesting GERD. These patients were selected according to the order of hospital admission for examination.

The patients in both groups were divided into two age categories, infants (1 month-12months) and children (>12 months); this was done because the reference values

and parameters for GERD diagnosis are different according to the age group to which the patient belongs. This classification also allowed an easier interpretation of data.

According to the differences in the clinical pictures, the patients were also divided into 3 categories: those with primarily digestive manifestations (recurrent regurgitation or vomiting, heartburn, abdominal pain, failure to thrive or poor weight gain, feeding refusal and irritability or persistent crying during feeding), those with mostly respiratory manifestations (persistent cough, recurrent wheezing, recurrent laryngitis), and those with mixed manifestations (both digestive and respiratory).

The presence of one or more of these signs and symptoms represented an indication for performing a 24-hour MII-pH monitoring at the time of admission.

MII-pH Monitoring

The test was performed in the hospital. The MII-pH monitoring system included a properly functioning MII-pH monitoring catheter and a portable recording device. The catheter had an outer diameter of 2.1 mm and contained 7 impedance sensors and one pH electrode. An infantile and a pediatric catheter were used, respectively, for patients younger and older than 2 years old. The catheter was inserted through the nose and was positioned so that the pH electrode was placed at the level of the third vertebra above the insertion of the diaphragm. In order to check for the correct position of the probe, fluoroscopic guidance was used for the procedure.

During the 24-hour period of measurements, the patients or their parents were asked to report any symptoms, mealtimes, and body position (prone or supine) by carefully completing a diary.

At the end of the recording period, the obtained data were downloaded into a computer and analyzed in both automated (using a dedicated software program) and manual-visual manner. The information written on the diary was also manually entered into the impedance tracings and analyzed.

The parameters measured by MII-pH monitoring were the reflux index, the total number of reflux episodes, the number of acid reflux episodes, number of weakly acidic reflux episodes and number of weakly alkaline reflux episodes. The test was considered to be positive or negative for pathologic GER according to the currently available guidelines parameters (Pilic et al. 2011).

Data analysis

Patients' data and MII-pH monitoring results were inserted into Microsoft Excel papers. The following variables were analyzed and compared between the two groups using the same program: signs and symptoms, frequency of pathologic reflux, frequency of pathologic reflux in different age groups (infants, children), type of reflux. ORs and 95% CI for association between prematurity and GERD were calculated using "Vassarstats: statistical computation website".

RESULTS

A total of 43 pediatric patients were enrolled in this study. In the study group, the youngest patient was 6 months old and the oldest was 9 years old, for a mean age of 2 years and 2 months. 11 were females and 8 were males. The majority of patients (58%) belonged to the children category while 42% were infants.

The control group had an equal sex distribution with 12 female and 12 male patients, the youngest was 3 months old and the oldest was 16 years old, with a mean age of 4 years and 2 months. As in the study group, children represented the largest part of the population (54%) while infants were 46% (Table 1).

The comparison of signs and symptoms between the two groups revealed that digestive manifestations were more frequent in the study group (89,47%) than in the control group (50%), while respiratory symptomatology was more common in the control group (33,3%) than in the study group (10,53%). None of the patients in the study group presented mixed manifestations, while in the control group these were identified in 16,67% of patients.

We also assessed the frequency of signs and symptoms in the two age categories (infants and children) of both groups.

Infants and children of the study group showed a similar symptomatology with predominant digestive manifestations.

In the control group, digestive manifestations were more frequent (63,64%) than respiratory and mixed ones in infants, while in children, respiratory signs and symptoms (46,15%) were more common than digestive (38,46%) and mixed ones (15,38%) (Tble 2).

The results of the 24-hour MII-pH monitoring were analyzed in order to objectively assess the presence of pathologic GER and to determine its characteristics in both groups.

The frequency of GERD was slightly higher in former premature patients than in patients who were born at term (63,16 vs 62,5). However, these results do not have a statistical significance that allows concluding that there's an increased risk of developing GERD among former premature patients (OR 1,02; 95% CI 0,2-3,5).

By comparing the results between infants of the two groups, we noticed that pathologic GER was more common in infants of the control group than in infants of the study group (63,6% vs 62,5%) (OR 0,9; CI 95% 0,22-4,25). Thus, it can be said that a history of prematurity

Table 1. Demographic characteristics of patients

	Study Group	Control Group
Age (years, median)	2,2	4,2
Infants (n, %)	8 (42%)	11 (46%)
Children (n, %)	11 (58%)	13 (54%)
Sex (M/F)	8/11	12/12

Table 2. Signs and symptoms of GERD in study group and control group

	Digestive	Respiratory	Mixed
Study Group	17/19 (89,47%)	2/19 (10,53%)	0
Infants	7/8 (87,5%)	1/8 (12,5%)	0
Children	10/11 (90,91%)	1/11 (9,09%)	0
Control Group	12/24 (50%)	8/24 (33,3%)	4/24 (16,67%)
Infants	7/11 (63,64%)	2/11 (18,18%)	2/11 (18,18%)
Children	5/13 (38,46%)	6/13 (46,15%)	2/13 (15,38%)

Table 3. Reflux characteristics at MII-pH monitoring

	Study Group	Control Group
Total number of reflux episodes (MII)	873	1359
Total number of acid reflux episodes (n [%])	456 (52,23)	848 (62,4)
Total number of weakly acidic reflux episodes (n [%])	333 (38,14)	506 (37,23)
Total number of weakly alkaline reflux episodes (n [%])	84 (9,62)	5 (0,37)
Reflux Contents		
Liquid	640 (41)	1012 (40)
Mixed	233 (15)	347 (14)
Gas	682 (44)	1154 (46)
Total number of reflux episodes (pH monitoring)	1585	2098
Reflux index (%)	4,7	5,49

was not a risk factor for GERD development in infants.

Pathologic GER was present in 63,6% of children in the study group and in 61,5% of control children. Our results revealed a slightly higher frequency of GERD in children of the study group, which, however, is not statistically significant enough to conclude that prematurity has represented a predisposing factor for the onset of GERD in this age group (OR 1.03; CI 95% 0,28-3,77).

MII-pH monitoring detected a total number of 873 reflux episodes in the 19 patients of the study group and a total of 1359 reflux episodes in the 24 patients of the control group. The majority of patients in both groups had acid reflux episodes; weakly acidic reflux was more frequent in the study group than in the control group and weakly alkaline reflux was detected in only 2 patients of the study group and in only 1 control patient. Both groups presented a predominance of gas reflux, followed by liquid and mixed type of reflux contents.

The main reflux characteristics in both groups are shown in Table 3.

DISCUSSION

This study wanted to find out if there exists a significant difference in frequency of pathologic GER between a group of pediatric patients with a history of premature

birth and a general population with signs and symptoms suggestive of GERD, thus determining an association between prematurity and higher risk of GERD development.

Our results showed an almost identical frequency of pathologic GER in the two groups, with a slightly higher prevalence of GERD in former premature patients (63,16% vs 62,5). However, it should be highlighted that, when the two groups were compared according to the age of the patients, pathologic GER was found in a higher percentage only in the children category of the study group compared to the children category of the control group; in contrast, an opposite result was obtained by comparing the infant category of the study group with that of the control group, the latter showing a higher frequency of pathologic GER than the former.

Despite this, the statistical analysis of our results didn't find any significant association between a history of prematurity and a higher risk of GERD development in our population.

MII-pH monitoring measurements were also used in order to assess the reflux characteristics in both groups and to determine if there were differences between them.

Even if acid reflux episodes predominated in both groups, they were more common in the control group than in the study group, the former also showing a greater average reflux index measured by pH monitoring.

The study group showed a higher frequency of weakly acidic and weakly alkaline reflux episodes than the control group, even if still far lower than acid episodes.

No significant differences between the two groups were encountered in the evaluation of reflux contents, with a predominance of gas reflux, followed by liquid and mixed refluxes.

In order to find out if there were differences in the presenting symptomatology, we examined the distribution of digestive, respiratory, and mixed manifestations in both groups. Digestive signs and symptoms dominated the clinical pictures of patients of both groups even if they were more common in former premature patients; the highest number of respiratory manifestations was detected in the control group, together with mixed manifestations that were completely absent in the study group. The symptomatology did not differ much in the different age categories - control children, who had mostly respiratory signs and symptoms, represented the only exception.

These findings correlate with the existing literature, according to which digestive or esophageal signs and symptoms represent typical manifestations of GERD (Sherman et al. 2009).

Few studies have evaluated the long-term risk of developing GERD in former premature patients and have given variable results.

Our findings are in accordance with 2 retrospective cohort studies, one conducted by Duerloo et al. (Deurloo et al., 2004) and the other by Kohelet et al. (2004), that didn't find a statistically significant correlation between premature birth and GERD development later in life.

On the other hand, a Swedish retrospective cohort study demonstrated a correlation between preterm birth and GERD or other gastric-acid related disorders by examining the association between gestational age at birth and anti-acid medication prescription in young adults. The authors found out that those who were born extremely preterm (22-27 weeks) had more than 3 times the odds to be prescribed anti-acid medications than those born at term, thus concluding that there is an association between premature birth and increased risk of acid-related disorders (Crump et al., 2012). Hence, these results are in contrast with our findings according to which prematurity and GERD are not significantly related.

Also, preliminary data of our study revealed a different trend to our latter results. GERD frequency was found to be higher in patients born at term (71,42%) than in former premature patients (56,25%) but, when a comparison between different age groups was done, pathologic reflux was found to be more frequent in former premature infants (57,14%) than in infants with no history of prematurity (44,44%). Thus, we concluded that prematurity represented a risk factor for GERD development only concerning infants (Galoș et al., 2015). These different data may be explained by a more restricted number of patients in the study population that may have influenced the statistical results.

Furthermore, a study that evaluated the risk of esophagitis in previously premature children and adolescents determined a strong association between premature birth and a higher risk of reflux esophagitis, therefore demonstrating a relationship between prematurity and GERD. The grade of association between prematurity and esophagitis varied according to age in this case as well: it was strong in patients aged 0-9, moderate in those aged 10-19 and no association was found in those older than 20 years old (Forssell et al. 2012).

Prematurity has also been related to an increased risk of Barrett's esophagus, for which GERD represents the predominant risk factor (Shiota et al., 2016). However, this study was conducted in adults and didn't find the association between prematurity and Barrett's esophagus to be mediated by GERD symptoms.

Subsequently, prematurity and GERD seem to be related somehow, even if a definite correlation between them has still to be established, given the contrasting findings present in the literature.

There were several limitations to the study. Our sample population was too small to obtain an ultimate epidemiological value; the selection of a bigger population would have increased the power of the study.

The information on signs and symptoms present in the database were mostly obtained by parents' report, given

the age of the patients. Description of the clinical manifestation may have been influenced by the parents' subjective perception. This, in general, represents a limitation to the clinical suspicion and diagnosis of GERD in pediatric patients who are not considered to be able to reliably report their symptoms under the age of 8 years old (Sherman et al. 2009).

This limitation may also have influenced the recording of symptoms during MII-pH monitoring period, in which the patients and their parents were asked to carefully notice and report any significant signs and symptoms on a diary, possibly affecting the interpretation of the test.

Another limiting factor was that the lack of precise data on gestational age at birth didn't allow assessing the risk of GERD in the different premature categories according to the classification of prematurity based on gestational age.

CONCLUSION

In conclusion, even if the findings of our study do not demonstrate an association between former premature birth and GERD development, the topic warrants further research. The established relationship between prematurity and GERD complications, like the above mentioned reflux esophagitis and Barrett's esophagus, mandates further investigations of GERD among previously premature infants and children. Indeed, the long-term duration of exposure of the esophageal mucosa to the noxiousness of the refluxate may put the patient at risk for life-threatening complications, which may be avoided if GERD is early detected. Future research may point towards establishing a definite association between prematurity and GERD and understanding its mechanism in order to provide a better and earlier surveillance and management of this category of patients.

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