Respiratory Medicine (2011) 105, 972–978

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Acid and weakly acid gastroesophageal refluxes and type of respiratory symptoms in children

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Received 19 November 2010; accepted 25 January 2011
Available online 18 February 2011

KEYWORDS
Multichannel intraluminal impedance;
Apnoea;
Asthma;
Respiratory manifestations

Summary
Objectives: To evaluate the association between the frequency of acid reflux (AR) and weakly acid reflux (WAR) and specific respiratory symptoms (RS) in childhood.
Study design: We retrospectively reviewed medical records of children with difficult-to-treat RS, not under acid suppressive therapy, and with a positive multiple intraluminal esophageal impedance (pH/MII) monitoring. To discriminate children with prevalent AR and WAR events, a ROC curve was designed and the distribution of the different RS in children with prevalent AR or WAR events was analyzed.
Results: A higher number of AR over WAR events was detected ($p < 0.0001$) but the WAR-to-AR events ratio progressively decreased with the age of the subjects ($p < 0.01$). Similar total number of reflux events was found in the three age group and in children with a more prevalent WAR or AR. The most prevalent RS, equally distributed among the three age groups, were persistent and/or nocturnal cough, wheezy bronchitis/asthma, and recurrent lower respiratory tract infections (RLRTI). Apnoea was most frequent in infants ($p = 0.036$). A higher frequency of RLRTI, but not of nocturnal cough or wheezy bronchitis/asthma, was shown in WAR as compared with AR patients ($p = 0.040$), and specifically those in the school-aged group ($p = 0.013$). Age and WAR were respectively identified as independent predictors of apnoea and RLRTI ($p < 0.05$).

Abbreviations: WAR, weakly acid reflux; AR, acid reflux; RS, respiratory symptoms; GER, gastroesophageal reflux; pH/MII, multichannel intraluminal impedance associated with pH-metry; SD, standard deviations; ROC, receiver operator characteristic; ORs, odds ratios; 95% CI, 95% confidence intervals; LCR, laryngeal chemoreflexes; LLM, lipid laden macrophages; BAL, bronchoalveolar lavage.

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2011.01.016

Conclusion: WAR events are common in children with gastroesophageal reflux and difficult-to-treat RS and often associated with RLRTI. These findings support the role of pH/MII monitoring in the evaluation of these patients and may explain the disappointing clinical results often observed with anti-acid treatments.

Introduction

The pathogenesis of gastroesophageal reflux (GER)-related respiratory symptoms is multifactorial, related to the frequency and duration of the reflux events but possibly also to the acidity of the refluxate which may be aspirated.[1,2] Because respiratory disorders and GER are both common in childhood and often co-exist, the causal relationship between these two conditions may be difficult-to prove also with the aid of supporting tests.[3] With the advent of multichannel intraluminal impedance associated with pH-metry (pH/MII), it has become possible to detect all GER episodes accompanied with a bolus movement and classify GER episodes according to their content (liquid, gas and mixed), pH value and proximal extension.[4] The possibility to measure not only acid, but also weakly acid refluxes and alkaline refluxes, has expanded the diagnostic power of pH detection alone and has expanded our knowledge on this medical condition, common in the pediatric population.[5,6]

In infants with GER and respiratory symptoms it was found that the majority of postprandial reflux episodes were not accompanied by a drop in oesophageal pH and that, because of the frequent feeding and subsequent buffering of gastric contents.[7–9] In contrast, in older symptomatic children, acid and weakly acid refluxes were reported to occur approximately at the same rate.[6,10–12]

Evaluating the possible connection between refluxes and respiratory symptoms, a frequent temporal association was detected in very pre-term infants between GER episodes (acid and weakly acid refluxes) and irregular breathing, with apnoea and/or oxygen desaturation.[9] In addition, it was demonstrated that cough-reflux association seems to be higher in infants than in older children[8] and that both acid and weakly acid reflux events may precede respiratory symptom in term infants and in children with unexplained cough.[13]

More challenging is the assessment of the causal association between acid and weakly acid reflux events and symptoms, when evaluating patients who may complain more than one respiratory complain. Indeed, a question that has not been previously addressed is whether a higher frequency of wheezy bronchitis, asthma, respiratory infections, laryngospasm and apnoea, in addition to cough, may be more often associated with acid versus weakly acid reflux events in children of different ages.

A retrospective study was therefore performed in infants, preschool-aged and school-aged children with GER and difficult-to-treat respiratory symptoms evaluated by oesophageal pH/MII monitoring. The number of acid and weakly acid reflux events was detected and, through a ROC curve analysis, children with more prevalent acid versus weakly acid reflux events were discriminated. The distribution of the different respiratory symptoms in children with more prevalent acid or weakly acid reflux events was then evaluated.

Methods

Patients

In this 2-yr retrospective study, we evaluated the clinical records of children admitted between January 2007 and December 2008 because of chronic or recurrent, difficult-to-treat, respiratory symptoms, found to have a 24 h oesophageal pH/MII monitoring positive, according to the criteria previously described.[11,14] Respiratory symptoms included: persistent and/or nocturnal cough, wheezy bronchitis/asthma, recurrent lower respiratory tract infections, laryngospasm and apnoea.[14] We excluded from the study patients with: i) prematurity; ii) neurological abnormalities; iii) swallowing disorders; iv) structural gastrointestinal abnormalities, such as pyloric stenosis, malrotation and annular pancreas; v) motility upper gastrointestinal tract disorders, such as achalasia and delayed gastric emptying; vi) airway or great vessel structural abnormalities; vii) recent (less than four weeks) or current respiratory tract infections. To avoid interference of anti-acid treatment on the frequency of acid versus GER events, children treated ever or in the previous eight weeks with acid suppressor (H_2-blockers or proton pump inhibitors) or in the previous week with antiacids or alginates, were not included in the study. The study population was subsequently divided into three age groups: (i) infants, $<$2 yrs old; (ii) preschool-aged children, 2—5 yrs old; (iii) school-aged children, $>$5 yrs old.

Access to health records complied with the Italian legislation and the study was approved by the Ethics Committee of the Gaslini Institute, Genoa, Italy.

Clinical assessment

Clinical data were collected uniformly in all children, according to the Gaslini Institute clinical protocols.[16,18] Specific tests were also performed to identify conditions such as ciliary dyskinesia, cystic fibrosis and immunodeficiencies. Clinical suspicion of GER warranting investigation was determined based upon: (i) presence of typical features or (ii) severe symptoms possibly related to GER. Indication for 24 h oesophageal pH/MII monitoring was discussed with the child's parents or tutors. When clinically indicated, multidetector computed tomography, fiberoptic bronchoscopy and/or oesophago-gastroduodeno endoscopy, were performed, as previously described.[14] All these investigations were carried out with full-informed, written parental consent.