Distress in Infants and Young Children: Don't Blame Acid Reflux

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ABSTRACT

Objective: The role of gastroesophageal reflux (GER) causing distress in infants is controversial but acid inhibitors are often empirically prescribed. We evaluated the relation between distress assessed by the Face, Legs, Activity, Cry, Consolability (FLACC) scale and GER in infants.

Methods: We analyzed multiple intraluminal impedance-pH (MII-pH) monitoring tracings of infants with persistent unexplained fussiness or distress. Symptoms occurring during investigation were scored by parents using the FLACC scale and were grouped as ''distress'' episodes.

Results: We recruited 62 children (ages 15 days to 23 months, median age 3.5 months). During MII-pH, 452 episodes of distress were registered: 217 (48%) were temporally associated with GER and 235 (52%) were not, with no difference in the median value of FLACC between the 2 groups. Infants with abnormal acid exposure index had a significantly lower FLACC compared with the group with acid reflux index $<7\%$ ($P < 0.001$). When associated with symptoms, GER occurred significantly more often before than simultaneously or after an episode of distress ($P = 0.001$). Age, proximal extension, and duration of GER did not correlate with FLACC scores. Episodes of distress associated with nonacid reflux presented a significant higher FLACC compared with the ones with acid content (FLACC 6 vs 5, $P = 0.011$). In infants, episodes of distress do not significantly correlate with GER.

Conclusions: No difference in infant distress was noted between proximal and distal GER. Non-acid reflux is perceived at least as painful than acid GER. Our results stress that acid inhibitors should not be started in infants presenting distress unless a clear association with acid GER is demonstrated.

Key Words: crying, distress, FLACC scale, gastroesophageal reflux, impedance, infant

An infographic for this article is available at: *http://links.lww.com/MPG/B880*.

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What Is Known

- The role of gastroesophageal reflux causing distress in infants is controversial.
- Proton-pump inhibitors are frequently administered to distressed infants, without a proper diagnostic work-up and despite evidence for absence of benefit from literature.
- The Face, Legs, Activity, Cry, Consolability scale is a validated tool to quantify for infant pain and distress.

What Is New

- About half of the episodes of crying and distress are temporally related to gastroesophageal reflux.
- Non gastroesophageal reflux acid is perceived even more painful than acid gastroesophageal reflux. Gastroesophageal reflux is not associated with infant distress symptoms based on the Face, Legs, Activity, Cry, Consolability score system.

The role of acid reflux in crying and distressed infants is debated since many years and still not clarified (1,2). Parents are often very anxious and distressed when their infant is crying because of fear for pain and/or of organic disease (3).

Inconsolable and persistent distress may, however, result from a normal developmental process over functional disorders to organic disease, such as food allergy, infection, trauma, or surgical conditions (4). Management of these episodes is challenging both for parents and physicians (2,4). Discrimination between normal and distressed behavior and infantile colic, related or not to gastroesophageal reflux (GER) or GER-disease (GERD) is challenging and influenced by perception, coping, and interpretation of caregivers and health care professionals.

Parental reassurance combined with dietary advice is often sufficient to reduce the anxiety of the parents and improve symptoms associated with GERD (2,5). Due to the fact that heartburn is the major presenting symptom of GERD in adults, distress and crying infants is often perceived by health care providers as the consequence of acid GER. Therefore, acid inhibitors are frequently prescribed in crying and distressed infants, presenting with or without regurgitation (2,6).

Recognition and quantification of pain is recommended by the World Health Organization to enable optimal treatment and alleviate needless suffering (7). The ''Face, Legs, Activity, Cry, Consolability'' (FLACC) scale is a validated measurement to assess pain in infants and young children (8–10). The objective of this study was to evaluate the relation between distress scored with the

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FLACC scale and GER assessed with esophageal multiple intraluminal impedance - pH monitoring (MII-pH) monitoring, considered to be the best diagnostic technique to measure acid and nonacid GER and identify reflux-related symptom association (2,11).

PATIENTS AND METHODS

Study Design

We conducted a prospective study consecutively including all infants and children under the age of 24 months referred for 24-hour multiple intraluminal impedance-pH (MII-pH) monitoring because of recurrent unexplained inconsolable distress as predominant or associated symptom of GER. According to the perception of the parents, no infant had sufficiently improved after at least 10 days of parental reassurance and education, behavioral and dietary advice including correction of volume intake, thickened and protein hydrolyzed formulas, as recommended by current guidelines on GER (2). Exclusion criteria were represented by: infants above 24 months of age or with symptoms or signs of acute infection, gastrointestinal malformations, previous gastrointestinal surgery, a known genetic syndrome, neurological impairment, naso-gastric tube feeding, dietary or pharmacological modifications in the last week.

An informed consent was obtained from all parents; the study was approved by the local Ethical Committee.

Aim

The primary outcome was to assess the temporal association between unexplained distress or crying and GER detected by MII-pH. The secondary outcomes were to evaluate the relation between the FLACC score and MII-pH results for acid versus nonacid reflux, the duration of reflux, esophageal extension, and the reflux index (percentage of time with esophageal pH < 4.0). The precise recording of onset and end of crying or distress episodes was assured using the internal clock of the MII-pH device.

Distress Assessment

Parents were instructed to fill in a symptom diary and the FLACC scale for all episodes of unexplained crying, distress or fussiness occurring during the MII-pH recording. The FLACC scale ranges from 0 to 10, with 0 representing ''absence'' and 2 ''maximal'' expression for any of the five items of FLACC (face expression, leg position, level of activity, kind of crying, and consolability) (8). Before the investigation, parents were instructed and trained on the use of the FLACC score by written materials and visual examples by 1 doctor and a nurse experienced in pediatric pain assessment. As parents have difficulties to distinguish crying, distress, and fussiness episodes, for the purpose of the study, all 3 symptoms were grouped together as ''distress''. The absolute and medians of the FLACC score were analyzed according to the presence/absence, duration, chemical composition, and esophageal extension of GER episodes.

Multiple Intraluminal Impedance - pH Monitoring

Participation in the study was proposed to the parents of all infants and children younger than 24 months who were referred for a MII-pH monitoring (Sleuth, Diversatek; Milwakee, WI) and who fulfilled the inclusion criteria. No parent refused participation. The technique, methodology, and analysis of MII-pH monitoring, and GER events were defined according to published criteria (11). Symptoms were considered as temporally associated with GER if they occurred 2 minutes before or after a reflux episode. Acid reflux was defined when esophageal pH was <4, whilst nonacid reflux was defined as a reflux episode with pH >4.0, including weakly acidic and alkaline reflux. According to the esophageal topographic distribution, proximal extension of reflux was considered when GER reached the first 2 (upper channels) MII rings (11,12). The automatic analysis of the tracings (Bioview software) provided the number, duration, proximal extension, and acid and nonacid content of all GER episodes. Symptom association probability (SAP; calculation of the statistical relationship between symptoms and reflux episodes) was used to evaluate the relation between episodes of distress and reflux episodes. By statistical convention, SAP at least 95% is considered as positive, suggesting that the relation between symptom and reflux is likely to be associated. All pH-MII tracings were then visually reviewed by a single author (S.S.) who was blinded to the result of the FLACC score. Periods with artifacts in MII-pH tracings were discarded from the analysis. Recordings were excluded if the duration of MII-pH was less than 20 hours or in the absence of crying, fussiness or distress episodes or lack of FLACC scoring. Pathological acid exposure was defined, according to pH-monitoring analysis, when total acid exposure rate was above 7% according to the 2009 ESPGHAN-NASPGHAN guidelines (13).

Statistical Analysis

Statistical analysis was performed using R version 3.6.2; Wilcoxon and *t*-test, as appropriate, were used to assess the difference of median and mean values of FLACC values according to the presence, absence, composition and proximal extension of GER. To account for the fact that more symptomatic children carry more weight in the analyses and possibly skew the results, we decided to perform the analyses in duplicate: associations between all distress episodes and clinical/baseline variables on 1 hand and the associations between 1 median FLACC score per patient and clinical/baseline variables on the other hand. Significant difference was considered when $P < 0.05$.

Sample Size

We aimed to recruit at least 60 infants, as estimated to be a sufficient sample of patients to assess the reliability and validity of FLACC in a previous study enrolling noncommunicating children (10).

RESULTS

Sixty-two patients (36 boys, median age 3.5 months, range 15 days to 23 months, mean age $\pm$ SD 5.5 ± 5.1 months) fulfilled the study criteria. During the MII-pH monitoring, 452 episodes of distress were recorded and scored with the FLACC scale by the parents. The number of episodes of distress ranged from 1 to 32 episodes per patient with a median of 5 episodes and a mean of 7.3 (SD 5.89). 217/452 (48%) distress periods were temporally associated with GER and 235 (52%) were not. The median value of FLACC (5) did not differ significantly between the distress episodes with and without temporal association with GER episodes ($P = 0.111$). According to the predefined time interval, GER preceded distress in 128/217 (59%) of the GER-related distress episodes, whereas GER occurred after the distress episode in only 41/217 (19%) of the GER-related distress episodes. GER and distress occurred simultaneously in 48/217 GER-related distress episodes (22%) ($P = 0.001$) (Fig. 1). The median FLACC score was 6 in the subgroup with GER preceding the distress, 5 in the subgroup with

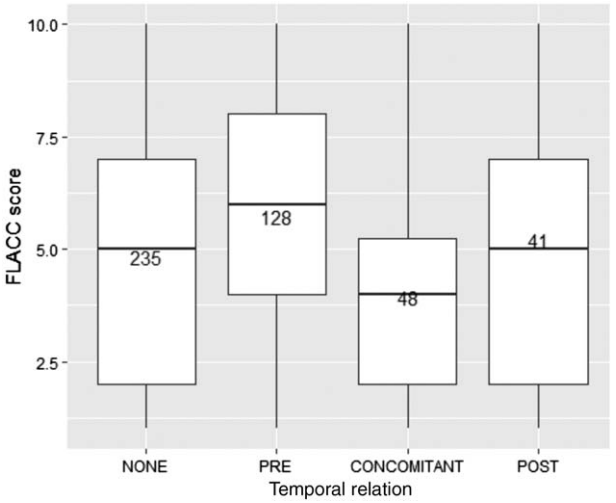

FIGURE 1. Comparison of Face, Legs, Activity, Cry, Consolability scores according to temporal association between distress and GER episodes assessed by MII-pH monitoring. Numbers in boxes: number of episodes of distress.

distress preceding GER and 4 in the subgroup with simultaneous GER and distress. After Tukey correction for multiple testing, the difference between GER preceding the distress and GER simultaneous with the distress remained significant ($P < 0.001$) as was the difference between GER preceding the distress and no temporal relation ($P = 0.013$); none of the other pairwise comparisons were significantly different (all P-values ≥ 0.13). A significantly negative relation between overall FLACC score and age was found ($r = -0.12$; 95% CI -0.21 to -0.03), which was no longer significant when the correlation with individual mean FLACC scores was made (95% CI -0.35 to 0.13).

Overall, 361 (80%) episodes of distress occurred in patients with acid reflux index <7% and 91 (20%) in patients with a pathological acid reflux index. The median FLACC value was significantly ($P < 0.001$) lower in the 12 (19%) infants with a pathological reflux index compared with the 50 infants (81%) with a normal reflux index. The same was still true ($P = 0.013$) when the median of the median FLACC score per patient was compared between both groups (median FLACC per patient in pathological acid exposure group 3 vs 6 in the nonpathological group). Conversely, 128 episodes of distress (28% of the total events, 59% of the temporally GER-associated events) coincided with nonacid reflux and had a statistically significant higher FLACC score compared with 89 acid reflux-associated events (FLACC 6 vs 5, $P = 0.011$). The duration of all GER episodes ranged from 3 to 1495 seconds, with a significantly negative correlation with the FLACC scores ($r = -0.23$; 95% CI -0.35 to -0.10).

SAP was positive in 16 infants (26%) with a median FLACC score of 6, in 8 infants for acid reflux (median FLACC 6) and in 8 infants for nonacid reflux (median FLACC 5). SAP was negative in 46 infants (74%), with and overall median FLACC in this group of 5 (significantly different from SAP-positive group: $P < 0.001$ and $P = 0.036$ when individual median FLACC scores were compared).

There were 136/217 (63%) episodes of distress with GER reaching proximal extension and 81 (37%) with distal GER, with no difference in overall FLACC score (5.5 vs 5; $P = 0.073$) or individual median FLACC scores ($P = 0.328$).

An overview of the FLACC scores according to the presenting symptoms, treatment, diet and MII-parameters is given in Tables 1 and 2.

DISCUSSION

This is the first study to assess fussiness, crying, and distress in infants and GER with quantification of symptoms and evaluation based on simultaneous FLACC score and MII-pH impedance. In the study population of unexplained distressed but otherwise healthy infants, not responsive to at least a 2-weeks period of parental reassurance and dietary advice, we found a temporal association between crying and GER in half of the episodes of distress. No significant difference was noted in FLACC score between distress episodes associated with or without GER. FLACC scores were lower when associated with acid GER than with nonacid GER episodes (5 vs 6, respectively). As the FLACC score ranges from 0 to 10, this is a difference of 10%. Although the clinical impact of a score of 5 may be comparable with a score of 6, our findings certainly indicate that nonacid reflux is at least as painful as acid reflux, if not more. When distress episodes were temporally associated with GER, reflux occurred significantly more often and with higher FLACC score before the distress episode than simultaneously or afterwards. Duration of GER episodes and esophageal proximal extension of GER did not significantly influence FLACC scores. Age was not a factor significantly influencing FLACC score.

Proper pain assessment and management is an important patient-centered goal of the World Health Organization and one of the physician's main missions. Pain assessment should be integrated into all clinical care (7). Pain perception is a combination of biological, psychological, social, cultural, and spiritual factors. The way parents react and cope with their child's distress is as well related to all the above-mentioned variables.

Self-reported pain score and faces pain scales are considered the preferred methods for its measurement (14). Although the infant

TABLE 1. Face, Legs, Activity, Cry, Consolability scores according to clinical presentation

Symptom	N (%)	FLACC scores all episodes (n = 462) Median (Q1;Q3)	Median FLACC scores per patient (n = 62) Median (Q1;Q3)
Crying—yes	41 (66)	6.0 (4.0;7.0)*	6.0 (4.5;7.5)
Crying—no	21 (34)	3.0 (2.0;6.0)	4.5 (2.5;6.5)
Regurgitation—yes	25 (40)	6.0 (4.0;7.0)*	6.0 (4.5;7.5)
Regurgitation—no	37 (60)	4.0 (2.0;7.0)	5.0 (2.0;7.0)
Feeding problems—yes	17 (27)	6.0 (2.0;8.0)	6.0 (4.5;8.0)
Feeding problems—no	45 (73)	5.0 (2.0;7.0)	5.0 (3.0;7.0)
Respiratory symptoms—yes	41 (66	4.0 (2.0;6.0)*	5.0 (2.0;6.0)
Respiratory symptoms—no	21 (34)	6.0 (4.0;8.0)	6.0 (4.5;7.5)

FLACC = Face, Legs, Activity, Cry, Consolability score; GER = gastroesophageal reflux.
*Significant difference between "yes" and "no" group ($P < 0.01$).

TABLE 2. Face, Legs, Activity, Cry, Consolability score according to different treatment, diet, and MII-pH parameters

Factor	Group	No patients	%	Distress episodes	Median FLACC
GER treatment	None	40	64	323	5
	PPI	5	8	32	7,5
	Ranitidine	8	13	61	6
	Alginate	8	13	35	5
	Domperidone	1	2	1	7
Feeding	Breast milk	21	34	163	5
	No breast milk	41	66	289	5
GER extension*	Proximal	41	66	136	5,5
	Distal	36	58	81	5
GER occurrence*	GER pre	45	73	128	6
	GER post	25	40	41	5
	GER simultaneous	24	39	48	4
GER content*	Acid	35	56	89	5
	Nonacid	44	71	128	6
SAP	POS	16	26	111	6
	NEG	46	74	341	5
SAP-positive	Acid	7	11	66	6
	Nonacid	8	13	38	5
	Acid + non-acid	1	2	7	6

FLACC = Face, Legs, Activity, Cry, Consolability score; GER = gastroesophageal reflux; NEG = negative; POS = positive; SAP = Symptom association probability.

*The sum of patients exceeds the total number of 62 as many infants showed episodes of different groups.

GER questionnaire was developed as a questionnaire to diagnose GERD in infants presenting with a variety of symptoms, including regurgitation and vomiting (15), FLACC was developed to validate distress and pain. Therefore, FLACC was more appropriate for our study population. In children younger than 6 years and in noncommunicating patients, FLACC has been demonstrated to be a simple and valid score (9,10). Nurses preferred the use of FLACC compared to other scales for its ease of use and pragmatic qualities (16). During the last two decades, prescriptions of acid inhibitors dramatically increased in infants presenting with crying and distress, without an objective demonstration of GERD (2,17). Although acid suppression is effective in most children as treatment of erosive esophagitis and acid-related symptoms, several intervention trials and reviews have concluded to a lack of efficacy of proton pump inhibitors to decrease infant distress (2,6,18).

Therefore, empirical administration of acid inhibitors is not recommended in distressed infants because of unnecessary, and thus ineffective pharmacological treatment and incorrect labeling of GERD. Moreover, acid inhibitors do have well established adverse effects, such as small intestinal bacterial overgrowth, increased risk for gastrointestinal and respiratory infections, increased risk for allergic disorders, and (micro-)nutrient deficiencies (19).

'Although many infants with overt GER-disease present with fussiness, crying and distress, these symptoms are only seldom manifestations of GERD in the absence of regurgitation or vomiting. Nonacid and distal GER may also cause distress in infants (12,20). The volume refluxed and related esophageal distention as occurs in nonacid GER may cause distress (21). There is no evidence based on the results of our study that acid or nonacid reflux episodes need to be treated as neither are associated with symptoms using a validated scoring system.

Our study does have some limitations. First, it was based on a 24-hour recording in hospital setting that may not reproduce what happens in day-to-day real life. Expanding the period of recording and home-based registration may be more appropriate but almost impossible to perform. We instructed parents to try to reproduce the home situation, feeding, and sleeping periods as much as possible during the investigation. Second, the reflux-crying temporal association was based on a parental-reported symptom diary what is known to be suboptimal for symptom recording (2,11). Video and acoustic recording during MII-pH monitoring could provide a better identification of distress episode. This method is, however, expensive, time-consuming, and most of all not reflecting parental perception. Interpretation of MII-pH tracings could also be limited by pre-setting temporal association of a 2 minute window period and manual analysis. There is, however, no evidence-based optimal period of time for symptom-reflux association and 2-minutes window is classically considered for both manual and automatic MII-pH analysis. In addition, only 1 author with good expertise in MII-pH interpretation in infants, blind to the FLACC score, did read the tracings after automatic analysis to reduce observer variability, and potential bias of reporting data.

CONCLUSION

Half of the episodes of distress reported during MII-pH were associated with GER in our study population. When distress was GER-associated, it was more frequent with nonacid GER (59%). In our population, the FLACC score for nonacid reflux was statistically significantly higher than for acid reflux (6 vs 5; $P = 0.0011$), although this difference is unlikely to be clinically significant. These findings, however, suggest that volume or esophageal distention may play a role in symptom generation, especially as GER was shown to precede distress. Acid-blocking medication in distressed infants and young children should only be prescribed in patients in whom a temporal association between distress and acid GER has been demonstrated, as in the majority of patients, there is no association.

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