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Original article

Predictors of Gastro esophageal Reflux Improvement among Infants

Mohammed B. EL-Amir[1], Atef A. Mahmoud[1*], Hanan M. Abd-El Moneim[1], Osama M. EL-Asheer[2]
[1] Department of Pediatrics, Faculty of Medicine, Aswan University, Egypt
[2] Department of Pediatrics, Faculty of Medicine, Assiut University, Egypt

***Corresponding Author:**
Atef A. Mahmoud
E-mail:
atefhadad1975@gmail.com

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ABSTRACT

Background: Functional gastrointestinal disorders in infants and toddlers are common worldwide and cover a variety of disorders associated with chronic, recurrent symptoms attributable to the gastrointestinal tract, but not explained by structural or biochemical abnormalities. **Objectives**: This study aimed to explore the main predictors for reflux disease improvements among infants. **Methodology**: This cross-sectional study recruited 300 infants with reflux manifestations from the outpatient clinic of the Pediatrics Department at Aswan University Hospital from January 2021 till December 2022. **Results**: after adjusting for age and sex, the main independent predictors for GERD improvement among the studied cohort were weight, length, skin manifestation, growth faltering, CoMiSs score at baseline and at 3rd visit. Conclusion: When CoMiSs negatives the AR formula more evident than PPI finally domperidine having the least impact on improving GERD symptoms. CoMiSs Score is a simple, fast, and easy-to-use useful tool for screening infants who presented with recurrent or persistent GI manifestations including GERD symptoms.
Keywords: GERD, CoMiSs, CMPA, Nutritional Treatment

INTRODUCTION

Worldwide, functional gastrointestinal disorders (FGIDs) in infants and toddlers are prevalent. They include a range of illnesses characterized by persistent, recurrent gastrointestinal symptoms that are not explained by structural or biochemical abnormalities [1]. GER is considered a normal, physiological process, if it creates symptoms or consequences that are associated with severe morbidity, it may be a pathological condition called gastroesophageal reflux disease (GERD). Epidemiological studies suggested that GER occurs in approximately 50% of infants < 2 months of age, 60–70% of infants 3–4 months, and 5% of infants by 12 months of age [2].

GER and GERD may increase parental stress and worry and negatively impact both the parent's and child's quality of life [3]. There is a subpopulation of infants with cow's milk protein allergy (CMPA) that present with vomiting and regurgitation, symptoms that are identical to GER, according to several studies. Some authors state that there may be a causal connection between the two circumstances [4]. The overlap between gastrointestinal (GI) manifestations of (CMPA) and frequent (functional) GI complaints such as GERD a result of the absence of objective diagnostic standards for each of the entities. Although estimates place the prevalence of GERD associated with CMPA as high as 56%, there is no evidence to support this claim [5].

This study was conducted to look at the co-existence of CMA in a group of infants with GERD for the first time in our area. In these situations, it would be possible to rule out GERD brought on by CMPA without taking extra drugs. In babies, nutritional treatment is advocated as a first line of defense, whereas for early management in children, a

therapeutic trial with antacid medication is advised [6]. The purpose of the current study was to examine the key factors that predict GERD among the studied cohort with specific emphasis on the effect of cow's milk protein eliminated diet.

PATIENTS AND METHODS

Included in this cross-sectional investigation were 300 infants presented with manifestations of GERD presented to the pediatrics department's outpatient clinic at Aswan University Hospital during that time from January 2021 till December 2022. Sample size was calculated using G*Power 3 software, with a power of 95% and type I error of 5% (α=0.05 and β=95%) on two tailed test, the minimum required sample was 300 participants to detect an effect size of 0.1 in the prevalence of improvement [7]. Full term infant, aged 1 month to 1 year, with manifestations of GERD On the other hand, infants with suggestive metabolic, neurologic or any chronic illness, with previous NICU admission, with genetic, chromosomal disorder or any dysmorphic features, proved gastrointestinal disease or malformation were excluded from the study.

Procedure

All studied infants were subjected to full history tacking, clinical examination including anthropometric measures with detailed recording of growth rate in addition to any manifestation of faltering growth during the period of study. Cow's Milk-related Symptom Score (CoMiSs) scoring as an indicator for suspension of cow's milk protein allergy (CMPA) conducted for all studied infants at both first visit and re-done on third visit after one month of exposure to any line of management included in our study. All groups were evaluated initially regarding anthropometry, manifestation of gastroesophageal reflux and CoMiSs scoring. Further re-evaluation, CoMiSs scoring was re-done on the 3rd visit after a month of treatment.

Statistical analysis

The Statistical Package for Social Sciences was used to verify, code, and analyze the obtained data (8). Calculated using descriptive statistics are means, standard deviations, medians, ranges, and percentages. Significantness test: To compare the variance in frequency distribution amongst several groups, the Chi-square test was utilized. We'll use the Shapiro-Wilk test to check the normality of the data. The mean differences in continuous variables between groups were tested using the student t-test. To determine the important steroid sensitivity factors, multivariable logistic regression analysis was performed (Odds Ratio -OR-, 95% confidence interval -95% CI- and Likelihood Ratio Test – LRT). A p-value < 0.05 was considered significant.

Ethical considerations

Approval for this study was obtained from Institutional review board (IRB # 24356) of Faculty of Medicine, Assiut University hospital prior to study execution. In addition, all participants/caregivers received a written consent form. The informed consent was clear and indicated the purpose of the study, and their freedom to participate or withdraw at any time without any obligation. Furthermore, participants' confidentiality and anonymity were assured by assigning each participant with a code number for the purpose of analysis only. The study was not based on any incentives or rewards for the participants and was abided by the guidelines of Helsinki Declaration [9] and the STROBE guidelines [10].

RESULTS

The univariate predictors of improvement were demonstrated in table 1. Improvement was matched for age and sex (p=0.501 and 0.437). Unlikely, improvement was reported in higher percentage in groups IV and V (26.5% of the improved cases), and then group III (23.1%), group II (15.4%) and the least in group I (8.5%) (p<0.001) (Fig.1). additionally, cases with positive improvement were significantly (p=0.019) taller (59.8 ± 6.9 cm) than unimproved (57.8 ± 6.9 cm) (Fig. 2). For the presenting symptoms, improved cases

had significantly (p=0.007 and 0.037) higher prevalence of growth faltering and skin manifestations (65% and 38.5%) compared with those without improvement (49% and 30.6%.For the presenting signs, improved cases had significantly (p=0.021, 0.047 and 0.001) higher prevalence of skin manifestations, chest manifestations and growth faltering (38%, 63% and 61.5%) compared with those without improvement (28%, 56% and 42%). Regarding the CoMiSS score, positive results were significantly higher among cases with improvement at baseline (51% vs. 38%). This was inversed on the 3rd visit (improved, 2.6% vs. unimproved, 31%). Moreover, improvement was reported in higher percentage in groups IV and V (26.5%) (Either breast fed, or bottle fed with elimination of cow milk), then group III (23.1%), group II (15.4%) and the least in group I (8.5%). This association was statistically significant (p<0.001) (Table 2 and Fig. 3).

Table 3 showed the multivariable regression analysis of the significant predictors of symptom improvement. After adjusting for the age and sex, the final logistic regression model contained six predictors, weight, length, skin manifestations, growth faltering and CoMiSs score (baseline and on 3rd visit). In other words, with one kg increase in the patient's weight there was 52% decrease in the probability of improvement (AOR=0.48, 95% CI 0.32 - 0.72), this was statistically significant (LRT < 0.001). However, with one cm increase in patient's length there was 20% increase in the probability of improvement (AOR=1.20, 95% CI 1.10 - 1.31), this was statistically significant (LRT < 0.001). Moreover, those with skin manifestations on examination had 89% less liability for improvement (AOR=0.11, 95% CI 0.03 - 0.45) and this was statistically significant (LRT = 0.002). Likewise, those with growth faltering on examination were 2.2 times more liable for improvement (AOR=2.17, 95% CI 1.13 - 4.16) and this was statistically significant (LRT = 0.020). Regarding the results of CoMiSs score (using ≥ 12 points as a cut off), those with positive score at baseline were 5 times more probability for improvement (AOR=4.92, 95% CI 1.07 - 9.86) and this was statistically significant (LRT < 0.001). On the other hand, those with positive score on 3rd visit had 99.3%less chance for improvement (AOR=0.007, 95% CI 0.002 - 0.033) and this was significant (LRT < 0.001.

Table 1: Univariate Predictors of Improvement of GERD symptoms (A)

	^Negative (n=183)	^^Positive (n= 117)	P-value
Age/months	4.13 ± 0.2	4.33 ± 0.3	= 0.501*
Sex			
Male	96 (52.5%)	56 (47.9%)	= 0.437**
Female	87 (47.5%)	61 (52.1%)	
Treatment Group			
Group I	50 (27.3%)	10 (8.5%)	
Group II	42 (23%)	18 (15.4%)	
Group III	33 (18%)	27 (23.1%)	< 0.001**
Group IV	29 (15.8%)	31 (26.5%)	
Group V	29 (15.8%)	31 (26.5%)	
Maternal Age/years	24.89 ± 4.7	25.04 ± 4.6	= 0.785*
Weight/kg	5.70 ± 1.5	5.79 ± 1.4	= 0.610*
Length/cm	57.86 ± 6.9	59.80 ± 6.9	= 0.019*

*Independent t-test was used to compare differences in means between groups.

**Chi-square test was used to compare differences in frequency between groups.

^Negative = no or insignificant improvement of GERD symptoms

^^Positive = significant improvement of GERD symptoms

Table 2: Univariate Predictors of Improvement of the studied groups (B)

	^Negative (n=183)	^^Positive (n= 117)	P-value
Symptoms			
Spitting	174 (95.1%)	111 (94.9%)	= 0.568*
Vomiting	135 (73.8%)	89 (76.1%)	= 0.380*
Crying	159 (86.9%)	90 (76.9%)	= 0.025*
Chest Manifest.	104 (56.8%)	86 (58.1%)	= 0.460*
Growth Faltering	90 (49.2%)	76 (65%)	= 0.007*
Skin Manifest.	56 (30.6%)	45 (38.5%)	= 0.037*
Diarrhea	70 (38.3%)	51 (43.6%)	= 0.212*
Constipation	16 (8.7%)	6 (5.1%)	= 0.173*
Signs			
Skin Manifest.	51 (27.9%)	44 (37.6%)	= 0.021*
Chest Manifest.	103 (56.3%)	74 (63.2%)	= 0.047*
Growth Faltering	77 (42.1%)	72 (61.5%)	= 0.001*
Positive CoMiss-1	70 (38.3%)	60 (51.3%)	= 0.026*
Positive CoMiss-3	57 (31.1%)	3 (2.6%)	< 0.001*

*Chi-square test was used to compare differences in frequency between group ^Negative = no or insignificant improvement of GERD symptoms ^^Positive = significant improvement

Table 3: Independent Predictors of Improvement: Multivariable Regression Analysis

Factor	Odds Ratio	95% CI*	LRT** P-value
Age	1.032	0.941 – 1.132	= 0.501
Sex (Male)	0.832	0.523 – 1.324	= 0.438
Weight/kg	0.477	0.316 – 0.721	< 0.001
Length/cm	1.200	1.099 – 1.311	< 0.001
Skin Manifestations (Sign)	0.106	0.025 – 0.454	= 0.002
Growth Faltering (Sign)	2.165	1.127 – 4.159	= 0.020
CoMiSS Score at Baseline	4.915	1.073 – 9.857	< 0.001
CoMiSS Score at 3rd visit	0.007	0.002 – 0.033	< 0.001

*CI= Confidence Interval

**LRT=Likelihood Ratio Test

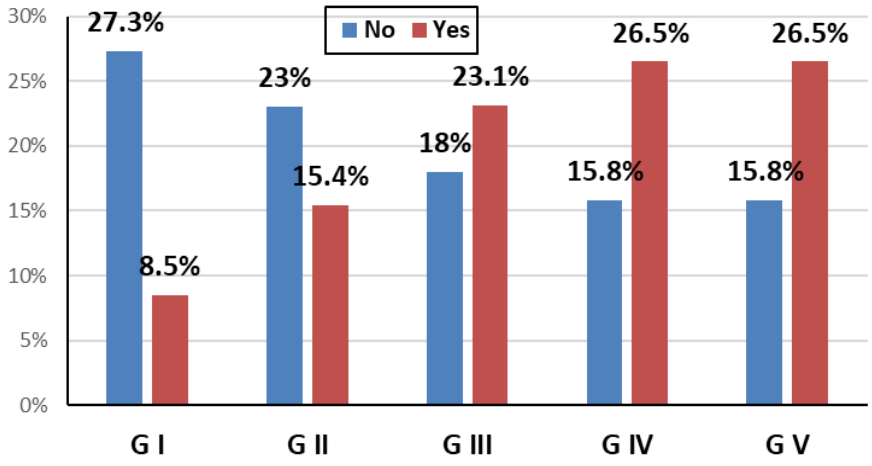

Figure 1: Relationship between Treatment Groups and Improvement Status

Yes =significant improvement of GERD symptoms No = no or insignificant GERD symptoms

Figure 2: Difference in the Patient's Length for Improvement Status

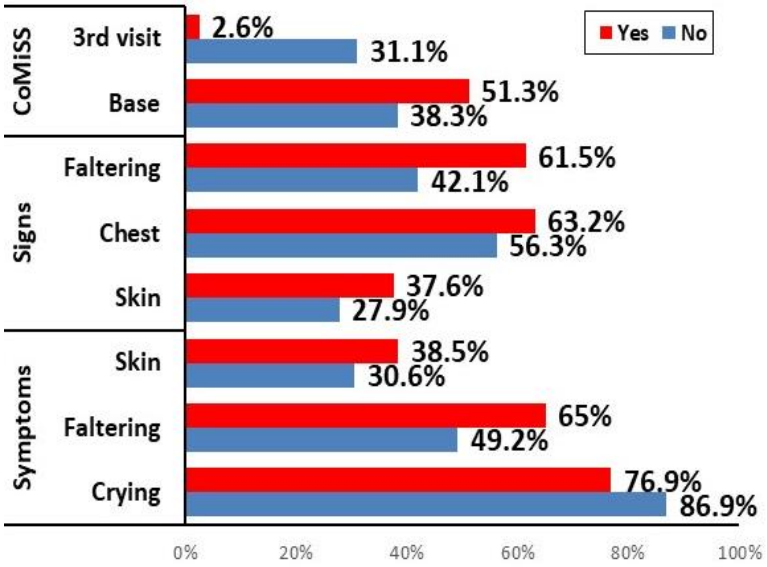

Figure 3: Univariate Predictors of Improvement of the studied groups

DISCUSSION

One of the most common complaints in pediatric gastroenterology and pediatric medicine facilities is gastroesophageal reflux disease (GER), a condition that primarily affects the esophagus [11]. The Rome IV criteria has defined Infant regurgitation as infant functional gastrointestinal disorders (FGIDs), which are defined as at least two episodes of regurgitation per day for at least three weeks in otherwise healthy infants between the ages of three and twelve months who do not exhibit retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing issues, or abnormal posturing [12].Regarding the various anti GERD measures used for 6 weeks from the initial visit for every case in this study, we aimed at determining impact of CMP elimination in GERD management either by CMP elimination from maternal diet (group V) or introduction of amino acid-based formula for bottle fed infants (group IV) and exclusion of any dairy products or other foods having cross antigenicity with CMP e.g. soya beans for whom complementary feeding had already been started before inclusion in the study and the impact of other non-surgical modalities of managements named introduction of anti-regurge (AR) formula for bottle fed infant (group III), the use of PPI (group II) and

administration of domperidone as a prokinetic agent (group).

The mothers who were exposed to CMP elimination from their diet referred to a nutrition specialist to compensate the eliminated food lists with others matched with dairy products eliminations. Non-significant relationship was found between CMP elimination via maternal diet restriction for breast fed infants or introduction of amino acids-based formula for bottle fed infants in progress of GERD symptoms. The mother should receive nutritional advice, 1000 mg of calcium per day, and 800 IU of vitamin D per day supplements while on the elimination diet [13]. In this study and regarding the outcomes after 6 weeks of interventions of patient symptoms and CoMiSs score, this score was applied on all cases of the study at first visit then 4 weeks later (third visit) and the results regarding GERD symptoms revealed that in groups IV and V where cow's milk protein (CMP) was eliminated, improvement of GERD symptoms was evident (51.7%) followed by group III (45%), group II (30%) and least in group I (16.7%).

This difference was significant and most of the improved cases in groups IV and V are CoMiSs Positive, and most of the improved cases in groups I, II and III are CoMiSs Negative. Re-application of CoMiSs Score at third visit revealed a significant decrease in the score points in CoMiSs Positive cases in groups IV and V and minimal changes in the score in other groups who were exposed to other interventions. This support the likelihood of two points, the first point was that there is a causal relationship between GERD and CMP and the second point was that CoMiSs is a valuable tool in suspicion of CMPA diagnosis. In conclusion our study revealed that, there was statistically significant difference in improvement of GERD symptoms between CoMiSs score positive cases and CoMiSs negative cases when exposed to CMP elimination. This in line with Omari et al who estimated that; Regardless of breast or formula feeding, the connection of CMA-GERD was found in 16–56% of individuals with persistent gastrointestinal symptoms and suspicion of GERD [14].

If there was no clinical improvement after a 4–8-week trial of dietary cow's milk protein exclusion, CMPA is unlikely [15]. However few publications covered the concomitant symptoms or occurrence of GERD and CMA. Nevertheless, due to the similarity of the symptoms and the dearth of reliable and practical diagnostic procedures, it is still difficult to distinguish between the two illnesses. According to the available According to epidemiological studies, less than 1% of breastfed or formula-fed infants will experience the expected casual coexistence of CMA and GERD. Infantile colic and reflux in breast-fed infants are rarely brought on by CMA as single presentations [16]. A study in Egypt by El-Shafie et al [17] revealed. A CoMiSs score of ≥12 to be the best cut-off point. CoMiSs is a useful technique for identifying infants who might benefit from a cow milk-free diet (CMFD), but it is insufficient to diagnose CMA with accuracy on its own.

Previous evidence has proved that CoMiSs is a simple, fast, and easy-to-use diagnostic tool which is suitable specifically for low- and middle-income countries. Moreover, CoMiSs has proven high accuracy, as it could diagnose 84.3% of the children that were confirmed via oral food challenge test, which indicates that CoMiSs can be utilized as a quick and accurate diagnostic technique for CMPA [18]. Regarding fed thickening in our study we used (AR formula) for bottle fed babies and we found a significant improvement in reflux, vomiting episodes and respiratory manifestations more evident - particularly- in CoMiSs negative cases and this matched with Ojha et al who reported that For babies who are formula fed, a thicker anti-reflux formula may be useful. Thickened feeds appear to be advantageous, according to a Cochrane study, even though only eight clinical studies were examined [19].

Even in infants suspected of GERD, According to the most recent recommendations, thickened formula should be taken into consideration as a first-line

therapeutic option for infants who are not exclusively breastfed [12]. However, it was reported that It is unclear whether the use of food thickeners helps other GER signs and symptoms or whether it causes negative effects in newborns, however it may somewhat reduce the frequency of overt regurgitation and vomiting in young children. Feeding modification should be considered even though there is insufficient data to warrant changing feeding quantities or intervals considered before more costly or risky interventions [20]. The impact of thickened formula on non-regurgitation symptoms is not clear [21]. Use of thickened formula is linked to a considerable reduction in visual regurgitation but not in measured acid reflux by MII-pH [18]. Alginates are recommended by the National Institute for Health and Care Excellence guidelines as a substitute for feed thickening agents in breastfed newborns or as a trial treatment in infants whose symptoms continue despite taking conservative measures [19] .

Regarding proton pump inhibitors (PPIs), the US Proton pump inhibitors (PPIs) are not beneficial in lowering GERD symptoms in infants younger than 12 months, according to a 2012 review by the Food and Drug Administration (FDA) of four randomized trials [22]. In the present study we use the FDA approved PPI, esomeprazole with accurately adjusted dosage 1–2 mg/kg/day administered 30–60 min before a feeding once daily, significantly improved GERD symptoms globally and more evident in CoMiSs negative cases and this is in accordance with a study reported that PPIs dramatically relieve heartburn sensations sooner and more completely than H2Ras and are a highly successful treatment for GERD. They also have little side effects [23].

In current study when we used domperidone as anti-GERD medication (group 1) and in comparison to other management modalities in the other groups we founded that domperidone having the lower impact on improvement of GERD symptoms Particularly in cases with positive CoMiSs, this was in line with Rosen et al. (2018), It is unclear whether domperidone use, when compared to a placebo, lessens infants' and kids' visual regurgitation/vomiting as GER signs and symptoms [20]. Domperidone and metoclopramide induce more side effects than a placebo, although there is no evidence that they lessen vomiting or apparent regurgitation. Domperidone's lack of efficacy in treating GER or GERD in young children has been attributed to a number of issues, including the dearth of trials and the high methodological heterogeneity of the research reviewed. The use of these medications is not advised due to a number of cardiac adverse effects, particularly extended QTc and arrhythmia. These medications appear to accelerate gastric emptying, reduce regurgitation events, and raise LES tone [24]. However, it was founded that No side effects were recorded during the research period, but there was a significant decrease in the proportion of patients who reported vomiting at the end of therapy in the group receiving domperidone compared to metoclopramide (p0.05) [25].

A 4-times-per-day, fixed-dose, anti-acid magaldrate/domperidone combination or domperidone alone during a month were the subjects of a double-blind, randomized, and comparative clinical trial research in adults. Magaldrate/domperidone combination was more effective than domperidone alone at reducing symptoms of worldwide esophageal and extra esophageal) reflux [26-27]. Prokinetics are thought to help children and infants with gastroparesis-related GERD and to hasten upper GI transit time. There are significant possible adverse effects of QT prolongation and extrapyramidal symptoms for the use of domperidone and metoclopramide, respectively [15].

Strengths and Limitations

Up-to-our knowledge , there are a limited number of studies comparing the CMP elimination with other non-surgical measures for management of Egyptian infants with GERD. This study contains useful new information for decision making in elimination of CMP for GERD management

in infancy. This study evaluates the effect of different non-surgical modalities.

The current study encountered some limitations, GERD manifestations didn't classify according to the severity, the studied cases had different types and patterns of feeding, and the diagnosis of CMPA should be confirmed by OFC test which was not documented in our study.

CONCLUSION

In conclusion, in failure of conventional GERD therapies a trial of 2 -4 weeks of CMP elimination is recommended. PPIs are recommended in cases of reflux-related erosive esophagitis. Prokinetics could be useful in cases of GERD as a result of gastroparesis and to hasten upper GI transit. The common comorbidity of GERD and CMA was documented in a significant percentage of cases with persistent gastrointestinal manifestations. There may be an under- or overdiagnosis of CMA and GERD. Therefore, the CMP elimination diet and anti-acid therapy are frequently launched based on empirical data and perhaps overly time-consuming. CoMiSS is a simple and practicable tool for early identification/screening for CMPA as 1ry cause for GERD.

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