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Original Article

Prevalence of Non-erosive Esophageal Phenotypes in Children: A European Multicenter Study

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Background/Aims
Since available data on pediatric non-erosive esophageal phenotypes (NEEPs) are scant, we investigated their prevalence and the phenotype-dependent treatment response in these children.

Methods
Over a 5-year period, children with negative upper endoscopy, who underwent esophageal pH-impedance (off-therapy) for persisting symptoms not responsive to proton pump inhibitor (PPI)-treatment, were recruited. Based on the results of acid reflux index (RI) and symptom association probability (SAP), patients were categorized into: (1) abnormal RI (non-erosive reflux disease [NERD]), (2) normal RI and abnormal SAP (reflux hypersensitivity [RH]), (3) normal RI and normal SAP (functional heartburn [FH]), and (4) normal RI and not-reliable SAP (normal-RI-not otherwise-specified [normal-RI-NOS]). For each subgroup, treatment response was evaluated.

Results
Out of 2333 children who underwent esophageal pH-impedance, 68 cases, including 18 NERD, 14 RH, 26 FH, and 10 normal-RI-NOS were identified as fulfilling the inclusion criteria and were analyzed. Considering symptoms before endoscopy, chest pain was more reported in NERD than in other cases (6/18 vs 5/50, $P = 0.031$). At long-term follow-up of 23 patients (8 NERD, 8 FH, 2 RH, and 5 normal-RI-NOS): 17 were on PPIs and 2 combined alginate, 1 (FH) was on benzodiazepine + anticholinergic, 1 (normal-RI-NOS) on citalopram, and 3 had no therapy. A complete symptom-resolution was observed in 5/8 NERD, in 2/8 FH, and in 2/5 normal-RI-NOS.

Conclusions
FH may be the most common pediatric NEEP. At long-term follow-up, there was a trend toward a more frequent complete symptom resolution with PPI-therapy in NERD patients while other groups did not benefit from extended acid-suppressive-treatment.
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Key Words
Children; Functional heartburn; Gastroesophageal reflux disease; Non-erosive reflux disease; Reflux hypersensitivity

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Introduction

Gastroesophageal reflux disease (GERD), defined as bothersome symptoms and/or complications resulting from gastric contents reflux into the esophagus or beyond,[1,2] is a chronic condition characterized by a heterogeneous spectrum of clinical manifestations.[3] Visible endoscopic breaks/erosions of the esophageal mucosa detected on esophago-gastro-endoscopy identify patients with erosive reflux disease (ERD).[3] Conversely, the presence of microscopic esophagitis without evidence of erosive esophagitis is not considered pathognomonic of GERD as it can also be found in up to 15% of asymptomatic healthy controls.[4] Nonetheless, an increasing body of evidence has shown that,[5-7] in a variable proportion of patients, GERD may exist in the absence of erosive esophagitis, as demonstrated by the presence of pathologic acid reflux on esophageal pH-(impedance) monitoring.[6,7] In this case the phenotype is defined as non-erosive reflux disease (NERD) and a different treatment response compared to ERD has been reported.[8-10] Whether endoscopy should be performed while the patient is on or off acid suppression is still debated. Adult guidelines on GERD suggest performing endoscopy off acid suppression therapy to allow a correct identification of the type of esophagitis.[11,12] The current European and Nord American guidelines on GERD[3] recommended performing a combined 24-hour multichannel intraluminal impedance and pH monitoring (MII-pH) in those children with normal endoscopy but persistent symptoms despite acid suppression therapy for 4-8 weeks. Based on the results of this diagnostic testing, the Rome IV criteria[3] on esophageal disorder define 3 distinct non-erosive esophageal phenotypes (NEEPs): (1) those with abnormal esophageal acid exposure regardless of symptom correlation (NERD), (2) those with normal esophageal acid exposure but a positive symptom association to acid or nonacid reflux (reflux hypersensitivity, RH), and (3) those with normal esophageal acid exposure and a negative symptom association (functional heartburn, FH).

Appropriate categorization of NEEP patients has important therapeutic implications since each subgroup has different pathogenic mechanisms and may respond differently to medical and surgical interventions.[13,14] Moreover, in clinical practice, physicians may face with a fourth subgroup of patients with normal esophageal acid exposure and a not-reliable symptom association, because of a very limited (less than 3) symptom episodes reported during the investigation characterization being an uncertain phenotype. Although this subgroup has not been defined by the Rome IV criteria, it may have a less likely response to acid-suppressive-treatment because of normal esophageal acid exposure.

So far, only a single retrospective pediatric study involving 45 children has assessed the prevalence of non-erosive reflux disease subgroups in pediatric ages.[15] In this European multicenter study, we aim at investigating the prevalence of the Rome IV NEEPs (NERD, RH, and FH), and of the subgroup with normal esophageal acid exposure and a not-reliable symptom association (undetermined phenotype), in a cohort of children who underwent both endoscopy and pH-impedance off-therapy. Moreover, the long-term outcome of symptoms and the response to treatment were examined in each subgroup.

Materials and Methods

The medical records of all children, aged 5-17 years, between January 2014 and April 2019, who underwent MII-pH within 6 months from a normal endoscopy for persisting typical reflux symptoms (such as heartburn or epigastric pain) despite acid suppression treatment (4 weeks), were retrospectively reviewed. The list of patients was obtained by the existing MII-pH electronic database of the 6 participating pediatric gastroenterology centers. Children were included if they underwent MII-pH off-therapy, within 6 months from a normal endoscopic assessment also performed off-therapy; therefore both investigations had to be performed off-therapy, that meant a wash-out period of at least 4 weeks before endoscopy, if previously treated with acid suppressive drugs. Before being submitted to MII-pH, patients should be off at least 2 weeks for acid suppressants, 72 hours if treated with prokinetics, and 4 hours if they had alginate. We considered a normal endoscopy in the absence of macroscopically visible breaks/erosions in the esophageal mucosa. The presence of microscopic esophagitis, defined as inflammatory cell infiltration, basal zone hyperplasia, papillary elongation, dilatation of intercellular spaces,[16] and evaluated in all patients by endoscopic biopsies, was not an exclusion criterion. Exclusion criteria were represented by one of the following: erosive or eosinophilic esophagitis; past history of gastric, duodenal or esophageal surgery; known esophageal motor disorders or any condition that interferes with the absorption, distribution, and metabolism of drugs (eg, celiac, inflammatory bowel disease); systemic disease (eg, diabetes mellitus, peripheral and autonomic neuropathies); neurological or mental impairment; major depression or behavioral disorder; drug or alcohol abuse; children on therapy with neuroleptic agents or any antidepressant during 6 months prior to enrollment; and children not fulfilling the inclusion criteria.

Collected data from medical records included demographic, reported symptoms before and after diagnostic testing, macroscopic and histologic endoscopic findings, and MII-pH results.

MII-pH was performed and analyzed in each hospital as previously described.[3,17-20] The MII-pH collected data included: number, characteristics and proximal extension of reflux episodes, reflux index (RI), number and type of symptoms reported during recording, symptom association probability (SAP), post reflux swallow induced peristaltic wave (PSPW), and mean nocturnal baseline impedance (MNBI).

The reflux index (RI), defined as the total percent time of acid exposure, was considered abnormal if pH $<$ 4 for $>$ 5% of the study duration.[17-20]

The symptom association probability (SAP) index, currently recognized as the most accurate statistical parameter for reflux-symptom association analysis,[21] was considered positive when $>$ 95%. The minimum number of symptoms to produce a reliable analysis is still debated and is related to the type of symptoms and the method of recording.[22] Nevertheless, it is widely recognized that the fewer the number of symptoms reported, the less reliable the SAP becomes.[23] Thus, in our study we considered as not-reliable SAP when the symptom was reported less than 3 times during the MII-pH. Based on MII-pH results, we categorized the enrolled patients in 4 subgroups: (1) abnormal RI (NERD); (2) normal RI and abnormal SAP (RH); (3) normal RI and normal SAP (FH); and (4) normal RI and not-reliable SAP (normal RI not otherwise specified ["normal RI-NOS"]).

The post reflux swallow induced peristaltic wave (PSPW) was defined as an antegrade 50% drop in impedance starting in the most proximal impedance channel and reaching the most distal impedance channel, occurring within 30 seconds after a reflux event.[24] The PSPW index was then obtained dividing the number of PSPWs by the total number of reflux events.[25]

MNBI was assessed from the most distal impedance channel during night-time by calculating the mean impedance baseline among three 10-minute time periods (at 1, 2, and 3 AM) with no reflux episodes, pH drops or swallows.[26] According to previous published adult criteria, cutoff values for PSPW index and MNBI were 61% and 2292 Ω, respectively.[27]

Finally, a telephone interview was conducted to evaluate, in each subgroup, symptoms persistence 2 to 5 years after investigations. Parents or patients (when older than 12 years) were asked about the presence, partial ($>$ 50% decrease in frequency and/or intensity of symptoms) or complete symptoms resolution on or off treatment in the month before the recall, and in comparison with the symptoms occurring at the time of MII-pH.

Informed consent was obtained by parents of recruited children. The study was approved by the Ethic Committees (No. 256, 19th September, 2019).

Statistical Methods

Data are presented as percentage (%), mean ± SD, median with interquartile range, as appropriate. The normality of distribution for continuous variables was assessed with Shapiro-Wilk test. Continuous variables were analyzed with Student's *t* test or Wilcoxon signed rank test as appropriate. Comparisons between categorical variables were performed with either chi-square or Fisher's exact test as appropriate. Differences in the mean values (continuous variables) among disease phenotype groups were assessed with one-way ANOVA or Kruskal-Wallis test as appropriate. The adjusted effect of various factors on certain outcomes of interest were explored with the appropriate type of regression analysis. All *P*-values were 2 sided with *P* less than 0.05 being considered statistically significant.

Results

During the 5-year period, 2333 MII-pH impedances were performed in the participating pediatric centers and 68 children (median age 11 ± 3.5 years, 33 female) were identified as fulfilling the study criteria and were included in the analysis. Based on RI and SAP, patients were categorized into: NERD 18/68 (26.5%), RH 14/68 (20.6%), FH 26/68 (38.2%), and normal RI-not otherwise-specified (RI-NOS) 10/68 (14.7%) (Table 1). The prevalence of symptoms pre-endoscopy in the study population and the distribution of each symptom among different NEEPs are shown in Figure. Regarding pre-endoscopy symptoms and phenotypes, chest pain was significantly more frequent in NERD (6/18) and in normal RI-NOS (4/10), ($P = 0.020$), whilst chest pain was reported in only 1/26 FH children and in none of the 14 RH patients (Figure). When assessing the association between symptoms pre-endoscopy and gender, we found that heartburn was more frequent in females (22/33 vs 9/35, $P = 0.001$), while there was a trend not reaching statistical significance toward an increase complaint of abdominal pain in male (15/35 vs 8/33, $P = 0.120$).

No significant statistical difference was found when comparing phenotypes and gender, histology report, and persisting symptoms during treatment.

The prevalence of persisting symptoms during proton pump inhibitor (PPI) therapy among the different phenotypes is shown

Table 1. Demographic Characteristics Among Subtypes

	NERD	RH	FH	nl-RI-NOS	Total	*P*-value
Total n (%)	18 (26.5)	14 (20.6)	26 (38.2)	10 (14.7)	68 (100)	NS
Male n (%)	10 (55.5)	7 (50)	14 (53.8)	4 (40)	35 (51.5)	NS
Median age (IQR)	12.5 (8-14)	10.5 (8-12)	11 (6-13)	11 (9-16)	11 (8-13)	NS

NERD, non-erosive reflux disease; RH, reflux hypersensitivity; FH, functional heartburn; nl-RI-NOS, normal reflux index not otherwise-specified; IQR, interquartile range; NS, not significant.

in Figure. There was a trend without statistical significance toward an increased report of regurgitation, abdominal pain, and heartburn compared to the other persisting symptoms and an increased report of vomiting and chest pain in NERD patients.

The prevalence of reported symptoms during MII-pH in the entire study population and the distribution among different phenotypes is illustrated in Figure.

Endoscopy and Biopsy

Microscopic esophagitis was found in 28.6% of patients: in 33.3% (5/15) of patients with NERD, in 28.6% (4/14) of patients with RH, in 23.1% (6/26) with FH and in 37.5% (3/8) with normal RI-NOS; in the remaining 5 patients (3 with NERD and 2 with normal RI-NOS) the referral letter from outside hospital generically reported "normal histology" without a detailed histological description, therefore these 5 patients were not included in this subanalysis. No significant differences in distribution of microscopic esophagitis among groups were found.

Multichannel Intraluminal Impedance and pH Monitoring

The MII-pH results are shown in Table 2. NERD patients presented a higher median number of acid and total reflux episodes compared to the other groups and when comparing NERD to FH (respectively $P = 0.001$ and $P = 0.008$). Moreover, NERD patients presented a higher median duration of the longest reflux episodes, statistically significant when comparing NERD to FH ($P = 0.004$), and a higher number of proximal reflux episodes, comparing NERD to normal RI-NOS ($P = 0.001$). MNBI values were lower in NERD and in normal RI-NOS (statistically significant only between normal RI-NOS and RH and FH) (Table 2). PSPW index was lower in NERD children compared to other phenotypes with no statistical difference among NEEPs (Table 2). In the NERD group, 33.3% (6/18) of patients had a positive SAP. RH had positive SAP only for acid reflux-associated symptoms. Regarding the reported symptoms during pH-MII (Figure), we did not found differences in the distribution of symptoms among subgroups and according to age.

Telephone Interview

At recall (mean ± SD follow-up duration: 28.8 ± 21.8 months) data of 23 patients (10 female, 8 NERD, 8 FH, 2 RH, and 5 normal RI-NOS) were available. Among them, 17 were treated with PPIs: 13 only PPI (6 with NERD), 2 combined with magnesium alginate, 1 was also on benzodiazepine plus anti-cholinergic drug, and 1 on citalopram; 3 patients were treated only with magnesium alginate (1 FH, 1 RH, and 1 normal RI-NOS) (Table 3). In the last month of follow up, there was no need of therapy in 13 patients (4 NERD, 4 FH, and 5 normal-RI-NOS) and the need of a course of treatment in 3 NERD and in 4 FH patients, while 1 RH patients was treated as needed. A complete symptom resolution was observed in 9/23 (39.0%) children: 5/8 (62.5%) NERD, in 2/8 (25.0%) FH (1 treated also with benzodiazepine plus anticholinergic), and in 2/5 (40.0%) normal RI-NOS (1 treated with the addition of citalopram). There was a partial symptom resolution in 3/8 (37.5%) NERD and in 6/8 (75.0%) FH, in 1/2 (50.0%) RH and in 1/5 (20.0%) normal-RI-NOS (Table 3).

Discussion

To the best of our knowledge, this is the largest described cohort of children with NEEPs based on the Rome IV-criteria. Increasing evidence suggest the existence of a phenotypic spectrum of GERD, with multifactorial underlying mechanisms, leading different symptom perception and possible treatment response.[28] The most common presentation of GERD at any age is non-erosive reflux disease, which has recently characterized in 3 distinct phenotypes (ie, NERD, FH, and RH) by the Rome IV esophageal criteria.[3,14] The prevalence of erosive esophagitis is even lower in children compared to adults.[29,30] So far, only a single pediatric study[15] examined the NEEPs prevalence by using the Rome IV criteria: among 45 children aged ≥ 5 years who underwent both endoscopy and pH-MII testing off PPI-therapy for typical gastroesophageal reflux symptoms, 44.0% were diagnosed as having FH, 29.0% as

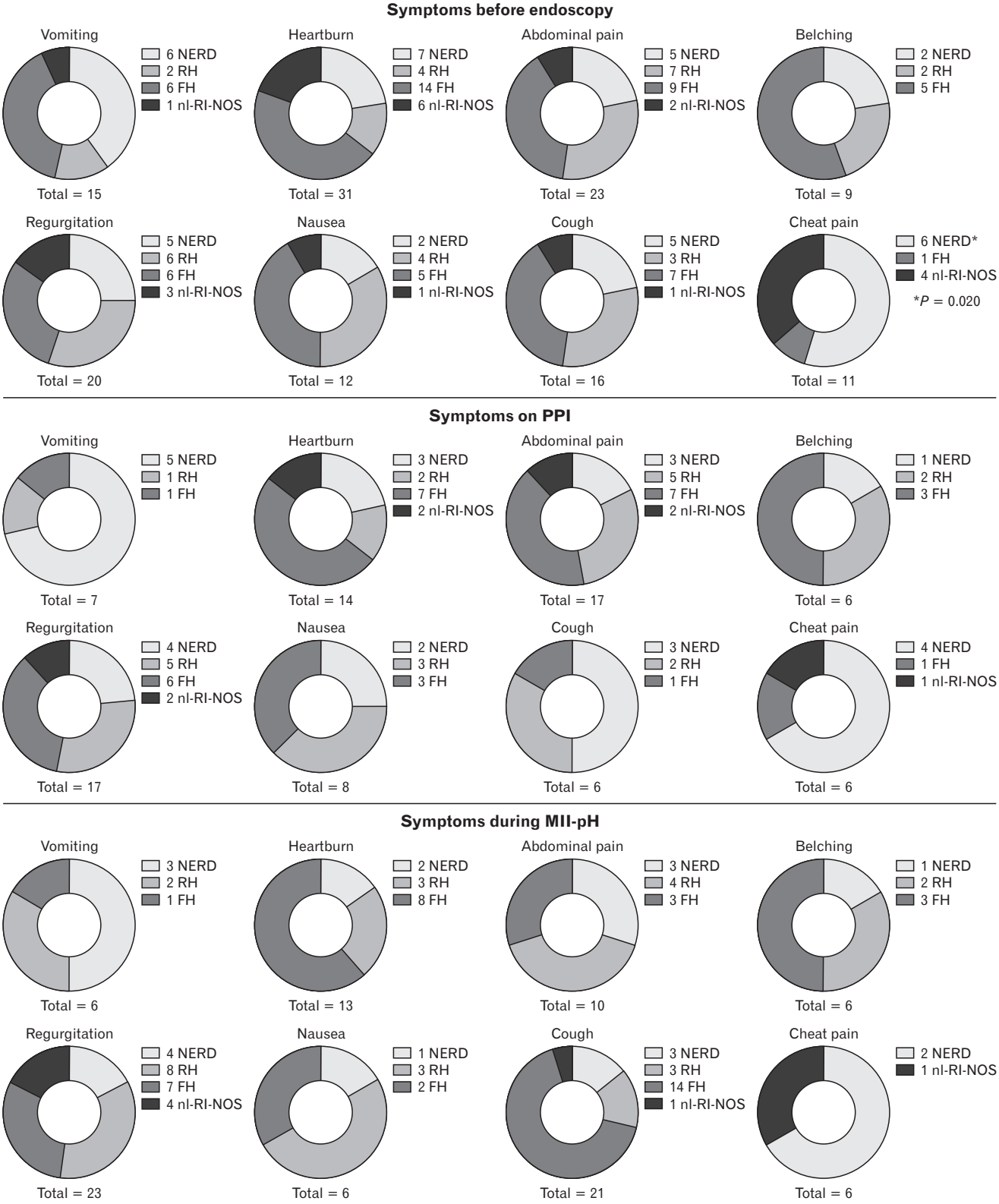

Figure. Prevalence of symptoms and distribution among different phenotypes. NERD, non-erosive reflux disease; RH, reflux hypersensitivity; FH, functional heartburn; nl-RI-NOS, normal reflux index not otherwise specified; PPI, proton pump inhibitor; MII-pH, multichannel intraluminal impedance and pH monitoring.

Table 2. Multichannel Intraluminal Impedance and pH Monitoring Parameters

	NERD	RH	FH	nl-RI -NOS	*P*-value[a]
Esophageal acid exposure time (RI) (median, IQR)	11.4 (8.3-14.7)	2.2 (0.5-3.3)	0.7 (0.2-1.4)	1.5 (0.8-3.6)	< 0.001[b,c,d]
Total reflux number (median, IQR)	87 (35.3-100)	41.5 (41.5-75.8)	28 (19.3-39.3)	24 (9.7-47)	0.008[b]
pH only events (median, IQR)	104 (81-121)	25.5 (10-42.8)	15 (3.7-25.3)	36 (9-57)	< 0.001[b,c]
Acid reflux number (median, IQR)	63 (33.3-80.8)	27.5 (10.3-41.3)	14.5 (4.2-26)	16 (3-32)	0.001[b]
Duration longest reflux (median, IQR)	20 (9.2-24)	2.6 (1.3-3.9)	1.9 (1.1-2.8)	7.9 (1.7-7.9)	0.004[b]
Proximal reflux episodes number (median, IQR)	40 (25-96)	32 (17.5-60.3)	14 (8-22)	8 (2.5-24.4)	< 0.001[b,d]
Distal MNBI (median, IQR)	1315 (1018-2832)	2724 (2273-3403)	2576 (2115-3014)	1446 (1165-1749)	0.003[e,f]
PSPW % (median, IQR)	42.6 (29.6-45.8)	56.3 (38.7-67.2)	52 (35.9-69.1)	59 (43.3-81.5)	0.125

[a]Comparisons with non-parametric ANOVA (Kruskal-Wallis test with Dwass-Steel-Critchlow-Fligner pairwise comparisons).
Levels of statistical significance: [b]NERD – FH, [c]NERD – RH, [d]NERD – RI neg-NOS, [e]FH - RI neg-NOS, and [f]RH - RI neg-NOS.
NERD, non-erosive reflux disease; RH, reflux hypersensitivity; FH, functional heartburn; nl-RI-NOS, normal reflux index not otherwise-specified; RI, reflux index; IQR, interquartile range; MNBI, mean nocturnal baseline impedance; PSPW, post reflux swallow induced peristaltic wave.

Table 3. Data at Follow-up

	NERD	RH	FH	nl-RI-NOS	Total
Total n (%)	8 (34.8)	2 (8.7)	8 (34.8)	5 (21.7)	23 (100.0)
Male n (%)	5 (62.5)	1 (50.0)	4 (50.0)	3 (60.0)	13 (56.5)
Treatment after MII-pH (n)	NERD	RH	FH	nl-RI-NOS	Total
PPI therapy and/or magnesium alginate	7	2	5	4	18
PPI and neuromodulators	0	0	1	1	2
No therapy	1	0	2	0	3
Treatment response at follow-up (n [%])	NERD	RH	FH	nl-RI-NOS	Total
Disappearance of symptoms:	5 (62.5)	-	2 (25)	2 (40)	9 (39.1)
Reduction of > 50% of symptoms:	3 (37.5)	1 (50)	6 (75)	1 (20)	11 (47.8)
Persistence of symptoms:	-	1 (50)	-	2 (40)	3 (13.1)

NERD, non-erosive reflux disease; RH, reflux hypersensitivity; FH, functional heartburn; nl-RI-NOS, normal reflux index not otherwise-specified; MII-pH, multichannel intraluminal impedance and pH monitoring; PPI, proton pump inhibitor.

RH and 27.0% as NERD, with the latter more commonly diagnosed in older children.[15]

Our multicenter study confirms, in a larger cohort of European children, that FH is the most common pediatric NEEP (38.2%,), followed by NERD (26.5%) and acid RH (20.6%). It is worth to note that in 14.7% of children with normal RI, SAP was not reliable because of almost absence of symptoms (< 3 episodes) during MII-pH; in this subgroup the phenotype was underdetermined (normal-RI-NOS). Nevertheless, even categorizing to one extreme all children with normal-RI-NOS as possible RH, the most common NEEP in our cohort would remain FH.

In contrast, studies conducted in adults found a higher prevalence (35.0-52.0%) of NERD phenotype, RH ranged from 14.0% to 35.0% and FH was identified in 22.0-30.0% of patients.[5,7,31]

Several different underlying mechanisms have been suggested to explain the discrepancy in non-erosive GERD phenotype prevalence between children and adults.[32] Mahoney et al[15,28] hypothesized a predominance of peripheral and central sensitization in children.[33,34] In an adult study, patient with FH have shown a significantly higher balloon distention mechano-sensitivity and acid perfusion chemosensitivity, when compared to either patients with NERD or healthy subjects.[35] Several genetic risk factors related to pain and molecular biomarkers have also been reported in association with increased symptom perception.[36-38] Moreover, in adult patients with FH, the afferent nerve fibers in the distal esophagus were distributed similarly to healthy asymptomatic controls, and both groups had significantly deeper nerve fibers in the mucosa, away from the luminal surface, compared to patients with NERD,[39]

supporting the hypothesis that heartburn in FH may have a distinct nociceptive pathophysiology. In contrast, Woodland et al[40] found significantly more superficial esophageal afferent nerves in adult NERD patients as compared to ERD patients, Barrett esophagus, and controls. Very recently,[41] it has been reported that in NERD children the esophageal mucosa displays deep lying nerve fibers and do not express the acid-sensing transient receptor potential channel vanilloid type 1 (TRPV1), in contrast to adults with NERD,[40] who showed a more superficial esophageal mucosa innervation and a TRPV1 overexpression. Different age-dependent levels of inflammation and/or repair mechanisms have also been considered.[41] The absence of severe inflammatory infiltration of the esophageal mucosa may explain the deep position of the afferent nerve fibers in children with NERD, since basal cell hyperplasia and papillary elongation would not move nerve fibers towards the luminal surface. In support of this hypothesis, there is a marked difference between the overall incidence of microscopic esophagitis in pediatric NERD (20.0%)[15] (28.6% in our cohort) compared to adult NERD (76.0%).[42] Moreover, impaired repair mechanisms in adults may also contribute toward the higher incidence of erosive esophagitis, 30.0% in adults[43] vs 12.4% in children.[29] Considering all these findings, NERD children seem to have less esophageal inflammation and deeper nerve fiber position compared to adults.

Esophageal hypervigilance, a form of hyperawareness and early detection of painful esophageal stimuli, is independently and significantly associated with symptoms severity and is consistent across reflux groups.[32] Nonetheless, in patients with FH, visceral neural pathways dysfunction and/or cortical processing alterations may also contribute and mediate esophageal hypersensitivity.[44] Interestingly, evoked cortical responses are produced by mucosal acid exposure in FH subjects prior to inducing heartburn.[45] Moreover, there is also a role for brain-gut interplay in symptom perception. Patients with FH more often report other functional gastrointestinal disorders, exhibit psychological comorbidity and somatization compared to heathy volunteers and NERD.[46-48] Stress has also been found to influence pain perception to esophageal stimuli.[49-51] FH is associated with significant psychosocial distress, anxiety, depression, and impaired quality of life.[52-54] However, if these underlying pathogenic mechanisms of FH and comorbidity may be more relevant in inducing symptoms perception in children as compared to adults remains a matter of research.

Regarding the correlation between pre-endoscopy symptoms and phenotypes, we found that chest pain was reported by 33.3% of NERD patients and in 4/10 of children with normal-RI-NOS but not in patients with RH. In line with Mahoney,[15] we did not find any other specific symptom profile that could be useful in prediction of reflux phenotype. In 62 adult patients, Kandulski et al[55] found no differences in reported symptoms (heartburn, regurgitation, or dyspepsia) between NERD, erosive esophagitis, and FH. In contrast, Savarino et al[56] showed a higher prevalence of heartburn in FH and of epigastric pain in NERD patients.

As for the symptom frequency and association during MII-pH, we did not find significant differences among the phenotypes. We noticed a trend of increased episodes of vomiting and chest pain in NERD and the association limited to acid reflux in RH, likely due to the scarcity of non-acid reflux episodes in this age group, as also shown by Mahoney et al.[15]

Regarding histological features, overall, 28.6% patients presented microscopic esophagitis, with a trend without statistical significance toward a more frequent identification in NERD and normal-RI-NOS. A correlation with NERD phenotype was reported in adult patients[55,57] but not in the previous pediatric study.[15]

In our population a lower distal MNBI was noted in NERD and normal-RI-NOS (median 1315 and 1446 respectively) compared to RH and FH. This result aligns with the presence of (microscopic) inflammation, reflux-induced impairment of mucosal integrity and acid exposure in NERD.[26,58-60] PSPW index was reported as able to discriminate between GERD and non-GERD adult subjects as well as NERD from FH.[61] We found a lower PSPW in NERD children compared to other phenotypes with no statistical difference among NEEPs.

Data on at least 2 years of follow-up were available for 23 children and 39.0% of cases reported a complete resolution of symptoms at recall, with a higher percentage of NERD patients responsive to PPI therapy (62.5%) compared to the other groups (25.0% in FH). Interestingly, 1 patient with FH was treated successfully with an association of benzodiazepine and anticholinergic, and 1 patient of the normal-RI-NOS group improved with the addition of a neuromodulator (citalopram). Thus, extending PPI therapy seems not appropriate for subgroups other than NERD patients and acidic RH, while other phenotypes may benefit from different treatment. In particular, in patients with normal-RI-NOS, extending PPI therapy seems not appropriate for unresponsive patients and different treatment such as neuromodulators may be indicated.

The enrolling criteria, accountable for the small sample size of our study, together with the retrospective design and the limited number of cases at follow-up, are significant pitfalls of our study, limiting the possibility to draw definitive conclusion, especially on treatment efficacy. However, by restricting the analysis to children who underwent both endoscopy and MII-pH off acid suppression

treatment, we were able to properly characterize the NEEPs and avoid the inclusion of possible other disorders such eosinophilic esophagitis.

In conclusion, we confirmed the existence of different NEEPs in children, with the most common phenotype being FH. A complete symptom resolution with PPI therapy occurs more frequently in NERD patients while other phenotypes do not benefit from extended acid suppressive treatment. Further prospective studies are needed to confirm these observations and to identify the best targeted therapeutic approach for each NEEP (eg, neuromodulators, complementary therapies), which still remains an unmet clinical need.

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