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THE SIGNIFICANCE OF DIFFERENT METHODS FOR DETECTION OF GASTROESOPHAGEAL REFLUX IN CHILDREN

ZNAČAJ RAZLIČITIH METODA ZA OTKRIVANJE GASTROEZOFAGUSNOG REFLUKSA KOD DECE

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Abstract

Symptom-based diagnosis of gastroesophageal reflux disease (GERD) is not specific due to high prevalence of disorders that can mimic GERD. Conventional pH monitoring, combined pH-MII (multiple intraluminal impedance) monitoring and esophagogastroduodenoscopy are diagnostic methods most frequently used in children.

Combined pH-MII monitoring is the most accurate diagnostic method for detecting GERD in children, which tends to become the gold standard. In infants and probably in children with extraesophageal symptoms, MII gives the greatest contribution to the validity of pH-MII monitoring. High prevalence of functional heartburn, in children older than 8 years, suggests the importance of pH-MII monitoring in this age group as well. The majority of studies showed age differences in the chemical composition of refluxate. Weakly acid reflux is more common in infants and is often associated with symptoms, whereas acid reflux is more common in older children and adolescent. Sensitivity of endoscopy is very low compared to pH-MII monitoring as a reference test. Although endoscopy is the method of choice for the confirmation of reflux esophagitis, pH-MII parameters are promising indicators of mucosal integrity, but further studies are needed.

The major problem with pH-MII monitoring is a lack of normative data for children. Therefore, the standardization is mandatory. For the present pH-MII monitoring has limited impact on treatment due to the absence of effective therapy for weakly acid reflux, suggesting that further studies should be directed in this direction.

Keywords:
Gastroesophageal reflux disease,
Children,
Esophageal pH monitoring,
Multichannel intraluminal impedance,
Endoscopy

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Sažetak

Dijagnoza gastroezofagusne refluksne bolesti (GERB), zasnovana na simptomima, nije specifična zbog visoke prevalencije poremećaja koji mogu da oponašaju GERB. Najčešće korišćene dijagnostičke metode kod dece su konvencionalni pH monitoring, kombinovani pH-MII (multikanalna intraluminalna impedansa) monitoring i endoskopija.

Kombinovani pH-MII monitoring je najtačniji dijagnostički metod za otkrivanje GERB-a kod dece, sa tendencijom da postane zlatni standard. Kod odojčadi i verovatno kod dece sa ekstraezofagusnim simptomima MII daje najveći doprinos validnosti pH-MII monitoringa. Visoka prevalencija funkcionalne gorušice kod dece starije od 8 godina ukazuje na značaj pH-MII monitoringa i u ovoj starosnoj grupi. Većina studija je pokazala starosne razlike u hemijskom sastavu refluksata (refluksnog sadržaja). Slabo kiseli refluks je češći kod odojčadi i često je povezan sa simptomima, dok je kiseli refluks češći kod starije dece i adolescenata. Senzitivnost endoskopije je, u poređenju sa pH-MII monitoringom kao referentnim testom, veoma niska. Endoskopija je dijagnostička metoda izbora za potvrdu refluksnog ezofagitisa, ali pH-MII parametri mogu da se smatraju potencijalnim markerima za procenu integriteta sluznice jednjaka.

Najznačajniji nedostatak pH-MII monitoringa je nepostojanje normativnih podataka za decu, zbog čega je standardizacija obavezna. Za sada pH-MII monitoring ima ograničen uticaj na lečenje GERB-a, pre svega zbog nedostatka efikasne terapije za slabo kiseli refluks, što ukazuje na to da dalja istraživanja treba usmeriti u ovom smeru.

Ključne reči:
gastroezofagusna refluksna bolest,
deca,
pH monitoring,
pH-MII monitoring,
endoskopija

Introduction

Gastroesophageal reflux (GER), retrograde flow of gastric contents into the esophagus, is a physiological phenomenon that appears in healthy children several times a day, especially after meals (1,2).

Gastroesophageal reflux disease (GERD) in children is defined by presence of troublesome symptoms and/or complications due to reflux of gastric contents in esophagus (1,2).

Reflux esophagitis, caused by acid reflux, is presented with endoscopically visible breaks in the distal esophageal mucosa (3).

Most common GER symptoms are age dependent. Extraesophageal (EE) symptoms are more common in infants and young children (1-5 years old) (4), whereas classical gastrointestinal (GI) symptoms are more often present in older children and adolescents (5). The most prevalent GER symptoms in infants are regurgitation with or without vomiting, and irritability, whereas in children and adolescents heartburn, epigastric pain and regurgitation (6). Unfortunately, symptom-based diagnosis is not specific due to high prevalence of functional disorders and conditions that can mimic GERD, including functional heartburn, cow's milk allergy and eosinophilic esophagitis (7–9). The over-diagnosing of GERD in infants, based on symptoms, has led to over-prescription of proton pump inhibitors (PPIs) without proofs of their efficacy (10).

It is evident that there was a need to assess GERD in a more objective way, for that purpose pH monitoring, combined pH-MII (multiple intraluminal impedance) monitoring and endoscopy are diagnostic methods most frequently used in children. The significance of other methods, such as proton pump inhibitor (PPI) test, GI series, esophageal manometry, scintigraphy and echosonography, is limited. Since the "gold standard" for the diagnosis of GERD has not yet been formally established, the formulation of well defined criteria is an area of intensive research in pediatric gastroenterology.

Combined pH-MII monitoring: advantages and disadvantages

Conventional pH monitoring enables differentiation between acid and non-acid reflux. The most important parameter of pH monitoring is reflux index (RI) or total acid exposure index, defined as percentage of time during which esophageal pH is below 4 (11). This method is still the diagnostic method most frequently used for evaluating patients with typical and atypical GER symptoms, due to simpler and shorter analysis comparing to pH-MII monitoring, as well as lower costs. However, pH monitoring has several disadvantages, such as the inability to measure weakly acid, non-acid reflux, superimposed acid reflux, gas reflux, postprandial reflux, proximal reflux episodes, height reached by reflux and bolus clearance (12). All of these parameters are obtained by combined pH-MII monitoring (catheter system consists of pH sensor and 7 impedance electrodes representing 6 bipolar impedance channels) (11). Combined pH-MII monitoring enables better estimation of the temporal association between symptoms and reflux events than conventional pH monitoring (11). According to the guidelines, the association between reflux episode (RE) detected by impedance and symptoms is estimated by calculation of the symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP) (11).

Direct comparison of MII monitoring, pH-metry and manometry before and after meals has showed that all 3 methods simultaneously detected only 19% RE (13). The

MII detected 96% RE, manometry 76% RE, and pH-metry only 28% (13). In the recommendations of European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), pH-MII monitoring has been recognized as a superior diagnostic method than conventional pH monitoring and it is recommended to be used, instead of pH monitoring in children (1). Afterwards, several studies have shown that combined pH-MII monitoring is a more sensitive method for detecting RE than pH monitoring alone (5,14). It is now clear that a significant percentage of RE in infants and children is weakly acidic, and that weakly-acid reflux causes symptoms (5,14,15). Therefore, pH-MII monitoring is the most accurate diagnostic method for the detection and characterization of GER in children and infants.

The most significant disadvantage of combined pH-MII monitoring is the fact that the pH-MII parameters have not been standardized for children yet. The disagreement of some authors, related to the definition of pathological MII findings and criteria for establishing association between symptoms and RE, is evident (16). In the study of *Pilic et al.* ("The German Pediatric Impedance Group") pathological MII finding was defined if the following criteria were met: SI ≥50% or high RE (> 70 episodes in children above 1 year of age or 100 episodes in infants) (5). *Loots et al.* have defined a positive symptom association if SI and SSI are both positive or SAP is positive (17). *Hojsak et al.* choose two out of three positive criteria (SI ≥50%, SSI ≥10%, SAP ≥95%) for defining MII abnormality (14).

According to the current guidelines for the interpretation of pH-MII monitoring, the best parameter for the analysis of temporal association between symptoms and reflux is SAP, because it is least influenced by the absolute number of GER events and number of symptoms. In the study of *Pilic et al.* a moderate agreement of SI and SAP (Cohen kappa 0.54) has been shown (5). *Luthold et al.* showed poor agreement between SI and SAP, as well as between SI and SSI, and SSI and SAP in infants with irritability (16). Several problems are faced in establishing the true association of symptoms with Res, that are mainly related to symptom registration and validation of optimal time frames between the onset of symptoms and the occurrence of RE (11). SI, SSI and SAP are based on the percentage of symptoms that are associated with REs and in this way one or two REs associated with a significant, life-threatening event can be missed.

There are some disagreements when normal values of pH monitoring parameters are in question. Namely, in the ESPGHAN/NASPGHAN recommendations from 2009, it is stated that reflux index above 7% is considered pathological and RI below 3% normal, while RI is between 3% and 7% indeterminate (1). However, in the next two sentences was stated that abnormal esophageal pH monitoring has not been shown to correlate with symptom severity in infants and that in a study of infants with suspected GERD, an abnormal pH study (RI >10%) was associated only with pneumonia, apnea with fussing, defecation less than once per day and constipation. In the majority of studies concerning infants, RI>10% was taken as cut-off, although there are studies with different cut-offs e.g. 5% (18), 7% (19) or 12% (20). In fact, authors taking 10% as cut-off, referred to *Vandenplas et al.* findings from 1991 (21). In this study of 509 healthy infants, the percentile curve of RI during the first year of life showed that RI was 10% (95 percentile) and ranged from 13% at birth to 8% at 12 months. In the aforementioned ESPGHAN/NASPGHAN recommendations, as well as in the study of *Moussa et al.* from 2011, authors agreed that because symptom severity is not correlated with the severity of acid reflux, normal ranges should be deemed as guidelines for interpretation rather than absolutes (1,19).

Among three widely used pH-metry scores (DeMeester score, Boix-Ochoa score and Johnson-DeMeester score), the Boix-Ochoa score is the most accurate for the diagnosis of GERD in children (22). *Lupu et al.* have demonstrated that high sensitivity and specificity of all three scores, as well as very high correlation between DeMeester and Boix-Ochoa score ($r = 0.978$, $p<0.01$, 95% CI), suggesting that they may equally be used in pH studies (23). Johnson-DeMeester score showed a greater risk of false-negative results (23).

Comparison of different diagnostic methods for detection of gastroesophageal reflux disease

Sensitivity, specificity and predictive values of symptoms are low in comparison with other diagnostic methods. In a study of irritable infants, regurgitation had a sensitivity of 54%, a specificity of 71%, and positive predictive value of only 22.2%, when pH monitoring was taken as a gold standard (cutoff RI> 10%) (24). In the same study feeding problems had a sensitivity of 75% and specificity of 46% (24).

In the study from *Pilic et al.*, 45% of children with GERD were only MII positive, but pH negative (5). *Hojsak et al.* showed that 52.3% children with GI symptoms and pathological pH-MII findings would not be identified by pH metry only, without significant differences between age groups (14). Another study indicated the lowest value of sensitivity in infants (59.4%), and the highest in children over 8 years (76.4%) (25). In the same study about 40% of infants and children diagnosed with GERD according to abnormal pH-MII findings would not be identified by pH-metry only (25). RI, the number of pH detected acid reflux events and composite reflux are significantly higher in children over 8 years of age compared to younger children and infants (25). These results differ from the results of *Hojsak et al.* where no difference in pH parameters between the age groups was found (14).

In the above mentioned studies, up to 70% of children over 8 years of age, with GI symptoms suspected for GERD, were pH-MII negative, emphasizing the

high prevalence of functional dyspepsia in this age group (14,25). These results imply a low diagnostic value of GI symptoms in the differential diagnosis of GERD and functional heartburn, even in older children. However, based on experts opinion diagnosis of GERD, in adolescent and older children with a typical reflux syndrome (heartburn with or without regurgitation and epigastric pain), may be established based on symptoms, with the recommended use of PPI test (1). PPI test is not recommended for infants and young children. It is important to mention that reporting of symptoms is unreliable in children under the age of 8 years and even lower in infants and neurologically impaired children who are unable to report symptoms (7,26–30).

Results from different studies showed that children with respiratory symptoms were more likely to have a normal pH monitoring findings than children with GI symptoms. *Pilic et al.* (5) included 700 children (329 with respiratory and 325 with GI symptoms), of which 270 had a pathological finding of pH-MII monitoring. In this study, 58% of patients with GERD were diagnosed with MII monitoring, only in the respiratory symptoms group. Another study demonstrated that pH monitoring sensitivity (using pH-MII monitoring as a gold standard) in children with isolated EE symptoms was 38.1%, while in children with GI symptoms with or without EE symptoms was almost twice as high (25). Nevertheless, a study of 25 children with chronic respiratory symptoms showed high frequency of acidic REs and a very small number of weakly acidic REs (ratio 19:1), with a negative SI for all types of reflux and a positive SSI for acidic and weakly acidic reflux (31). Another study of 24 children with asthma showed the same frequency of acidic and weakly acidic reflux, without clear temporal association for most of the symptoms (32). Study of children with respiratory symptoms on PPIs revealed the correlation between symptoms and weakly acidic reflux, that was stronger in younger children (33). The limitations of these studies are small samples and selection bias. Several studies have shown pathological RI in children with asthma, but it has not been established whether acid reflux is the cause, consequence or aggravation factor (34,35).

Endoscopy is a highly specific (90-95%) method for diagnosing of GERB (14,36,37). The sensitivity of endoscopy is low and does not exceed 50% in different studies (referent test pH-MII monitoring) (14,25,38).

Parameters of pH-MII monitoring in different age groups

It is known that, compared to conventional pH monitoring, pH-MII monitoring provides more information on reflux episodes and their composition, and that infants have a higher number of RE (1). Several studies showed a greater number of total and acidic RE in older children (14), and a larger number of weakly acidic episodes in infants (39,40). *Francavilla et al.* showed a higher number of weakly acidic episodes in infants, without a difference in the total number of reflux events between the age groups (39). However, several studies have shown a higher number of total REs in infants than in older children (5,14,17). Analysis of chemical composition of refluxate in healthy adult volunteers revealed that one-third of REs are weakly acidic or non-acidic (41–43). In healthy children, data are missing, but for older children it is assumed to be the same as in adults. Numerous studies have shown that in symptomatic infants more than half of the reflux events are weakly acidic (5,14,25,44,45).

Studies have shown a higher percentage of proximal, especially weakly acidic, REs in infants (14,39). A higher percentage of proximal REs, and a better temporal association of symptoms and REs in infants, supports the fact that in infants, reflux is more often symptomatic. A study in 60 healthy adults demonstrated a higher percentage of proximal acidic RE than weakly acidic RE (34% *vs.* 24%) (42). In another study of children with persistent respiratory symptoms 75% of non-acidic REs were proximal compared with only 8.8% of acid REs. *Moussa et al.* showed that proximal acidic episodes are more frequent than weakly acidic in infants (46).

The role of pH-MII parameters in prediction of reflux esophagitis

Gastric acid is a key element of reflux, which leads to tissue injury, macroscopic or microscopic changes in the esophagus mucosa (47). In several studies, a possible correlation between clinical symptoms and endoscopic findings was investigated, but no association was established (26,48,49). Studies in adults have shown that macroscopic changes in esophageal mucosa are more common in patients with an elevated acid exposure index and/or a higher number of acid reflux events (50,51). Most studies did not show a correlation between the number of MII detected REs and endoscopic findings (48,49). Nevertheless, *Hojsak et al.* demonstrated that children with GI symptoms and endoscopically proven esophagitis have higher number of total MII detected REs compared with children with normal endoscopy (14). These results suggest that weakly acidic reflux may play a role in the pathogenesis of reflux esophagitis (14). Study by *Liu et al.* found that the best predictors of reflux esophagitis are DeMeester score ≥ 21 and the duration of the longest acid reflux ≥ 17 minutes, as well as the occurrence of acid reflux over 5 minutes (36). These results indicate that macroscopic changes of esophageal mucosa are more common in patients with increased exposure to acid, as previously reported in adult studies (52).

The post-reflux swallow-induced peristaltic wave (PSPW) index and esophageal baseline impedance (BI) are novel MII parameters used to evaluate esophageal chemical clearance and mucosal integrity (53). BI represent the resistance to alternating current not related to swallowing or reflux, and serves to estimate the integrity of the esophageal mucosa (54,55). The presence of esophagitis reduces BI primarily in distal esophagus (56). There is a strong negative correlation between RI and BI (57). Low BI due to

prolonged acid and prolonged bolus exposure is associated with reflux esophagitis (48). However, not only macroscopic changes, but also subtle changes such as dilatation of intercellular spaces seen in non-erosive reflux disease (NERD) result in low BI (54). Some authors suggest that BI can replace multiple endoscopies in patients with reflux esophagitis (58). PSPW (the number of refluxes followed within 30s by swallow-induced peristaltic waves divided by the number of total refluxes) expresses chemical clearance and improves the diagnostic efficacy of pH-MII monitoring (59,60). Namely, damaged chemical clearance is primary pathophysiological mechanism specific to GERD, not affected by either pharmacotherapy or surgical treatment, and not seen in the functional heartburn (59). Damaged chemical clearance is more pronounced in erosive esophagitis than in NERD (59).

Treatment based on pH-MII findings: future perspectives

It is clear that weakly acid and non-acid reflux, detected by pH-MII monitoring, can cause symptoms. However, the clinical relevance of these data is still debatable. The key problem is the lack of effective treatment for weakly acid and non-acid reflux. Combined pH-MII monitoring enables classification of patients with GERD and normal endoscopy into two groups: patients with NERD (pH positive) and patients with hypersensitive esophagus (pH negative, MII positive) (61). Patients with heartburn and normal pH-MII findings are classified into a group of patients with functional heartburn. A significant proportion of symptoms refractory to PPI is associated with both acidic and weakly acidic reflux, as well as with gas reflux (62). Namely, PPIs are the most effective drugs for acid reflux, especially for reflux esophagitis (1). However, PPI-refractory reflux esophagitis and PPI-refractory symptoms (without esophagitis) are common. The possible explanations are persistent acid reflux, epithelial barrier disorder, weakly acidic reflux, but also hypersensitivity and hypervigilance (63). A large percentage of patients with PPI-refractory symptoms are patients with hypersensitive esophagus and functional heartburn (63). As possible solutions for patients with hypersensitive esophagus inhibitors of transient lower esophageal sphincter relaxation and antireflux surgery are discussed in the literature, but further studies are needed (64). Some authors believe that further researches and treatment will be directed towards hyperalgesia, allodynia, hypervigelance and anxiety (63).

Conclusion

Combined pH-MII monitoring is the most accurate diagnostic method for detecting GERD in children, which tends to become the gold standard. The importance of combined pH-MII monitoring is greatest in infants. Although, endoscopy is the method of choice for the confirmation of mucosal lesions, pH-MII parameters are promising predictors of reflux esophagitis. However, further studies are needed. These findings could have great significance, especially in infants and young children in whom endoscopy is rarely performed, due to small diagnostic contribution and the risk of complications. The most significant disadvantage of combined pH-MII monitoring is the lack of normative data in children. Therefore, further validation and standardization of pH-MII parameters are mandatory. Despite of the problems concerning the lack of effective treatment for weakly-acid reflux, pH-MII monitoring gives us the answer to the question of whether the reflux is the cause of child's problems better than any available diagnostic method. Owing to pH-MII monitoring, we can spare the child of unnecessary testing and ineffective treatments. Therefore, based on current evidence we developed diagnostic algorithm for children with suspected GERD (**Figure 1**).

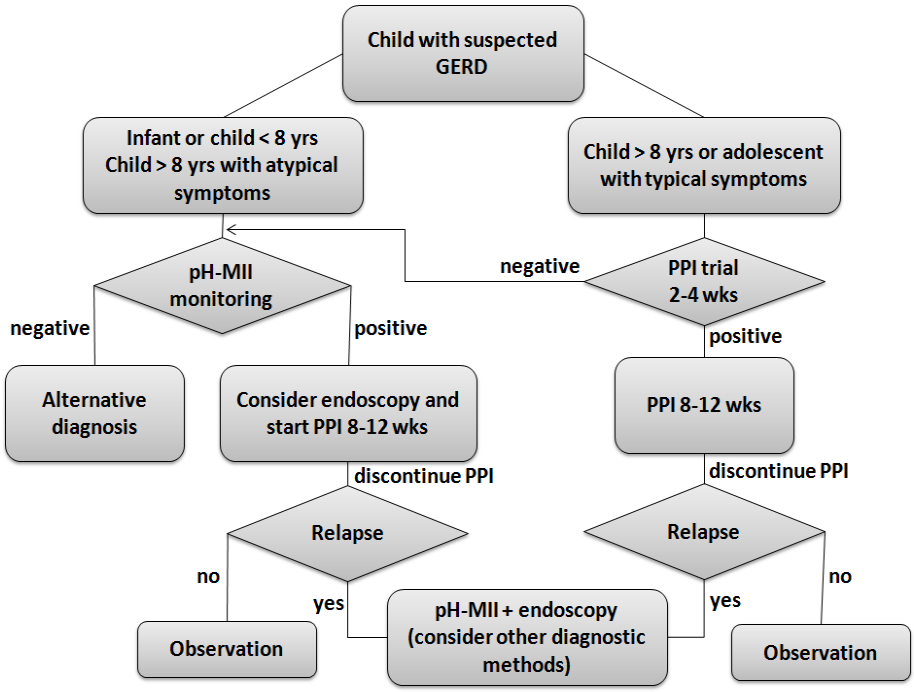

Figure 1. Diagnostic algorithm for children with suspected GERD

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