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REVIEW ARTICLE

The link between airway reflux and non-acid reflux in children: a review

Jeyasakthy Saniasiaya *, Jeyanthi Kulasegarah

University of Malaya, Faculty of Medicine, Department of Otorhinolaryngology, Wilayah Persekutuan Kuala Lumpur, Malaysia

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HIGHLIGHTS

- Airway reflux, a form of extra-esophageal reflux, has been linked to countless respiratory pathologies amongst children.
- Review of the literature revealed that non-acid reflux is the culprit behind airway reflux and other myriads of extra-esophageal manifestations in children.
- Non-acid reflux explains the exasperation faced by numerous otorhinolaryngologists following the futile outcome of devout usage of acid suppression in children to treat airway reflux.
- A recent surge in the implementation of multichannel intraluminal impedance monitoring amongst children has enabled the discovery of non-acid reflux.
- Multicentre international studies with a standardized protocol could improve scientific knowledge in managing non-acid reflux in airway reflux amongst children.

KEYWORDS
Gastroesophageal reflux;
Laryngopharyngeal reflux;
Airway reflux;
Non-acid reflux;
Children

Abstract
Objective: Airway reflux, a member of extra-esophageal reflux, has been linked to countless respiratory pathologies amongst children. The advent of novel instrumentation has enabled the discovery of non-acid reflux which was postulated as the main culprit of airway reflux. The objective of this review is to outline the association between non-acid reflux and airway reflux in children.
Methods: A comprehensive review of recent literature on non-acid reflux and airway reflux in children was conducted. Studies ranged from January 2010 till November 2021 were searched over a period of a month: December 2021.
Results: A total of eleven studies were identified. All studies included in this review revealed a strong link between non-acid reflux and airway reflux in children. 6 of the included studies are prospective studies, 3 retrospective studies, 1 cross-section study, and type of study was not mentioned in 1 study. The most common reported respiratory manifestation of non-acid reflux in children was chronic cough (7 studies). Predominant non-acid reflux was noted in 4 studies. The total number of children in each study ranges from 21 to 150 patients. MII-pH study was carried out in all studies included as a diagnostic tool for reflux investigation.

* Corresponding author.
E-mail: jeyasakthy@um.edu.my (J. Saniasiaya).
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Conclusion: Non-acid reflux is the culprit behind airway reflux as well as other myriads of extra-esophageal manifestations in children. Multicentre international studies with a standardized protocol could improve scientific knowledge in managing non-acid reflux in airway reflux amongst children.

Introduction

Airway Reflux (AR), an entity under the broad umbrella of extra-esophageal reflux, denotes regurgitation of noxious refluxate beyond esophagus trespassing the airway. AR is also termed as silent reflux as 70% of the affected population remains incognizant.[1]

Over the past years, we have witnessed a shift in the paradigm of how AR manifest. Firstly, the idiosyncratic evolutionary development of the human aerodigestive tract has been shown to pave the way for AR to take place. The first confounding evolutionary feature follows the development of speech and language. As the larynx enlarges and simultaneously descends adjacent to the upper esophagus and away from the soft palate, this close proximity to the laryngeal sphincter and expansion of the oropharynx has unwittingly aided refluxate to enter the airway. Akin to that, the concept of bipedalism which precisely was premeditated for humans, is yet another attributing factor for AR. The connection between the esophagus and stomach has advanced to a straight line from the initial right angle, removing the anatomical barrier preventing reflux when the lower esophageal sphincter opens.[1]

Secondly, the dogma that the acid component is the main pillar behind AR, has been questioned. Historically, reflux has been linked with gastric hydrochloric acid. Interestingly, a myriad of research has recently reported that non-acid reflux to be the main culprit of various AR.[2–12]

Thirdly, both acid and Non-Acid Refluxate (NAR) entering the airway has been shown to damage the delicate epithelial lining of respiratory epithelium, promoting alteration of respiratory histological features. The co-existence of the aforementioned three features leads to AR.

It is noteworthy that, besides AR, extra-esophageal reflux leads to entire anatomical alteration above the esophagus, causing sinusitis, middle ear effusion, otalgia, globus pharyngeus, sleep disordered breathing[13] as well as dental erosion in children.

Clinical implications stemming from AR amongst children include airway stenosis, inflammation of upper and lower airway, laryngospasm, acute life-threatening event, apnea, and jarringly sudden infant death syndrome. NAR has been linked to these numerous airway pathologies.[10] Traditionally, anti-reflux medications, notably Proton-Pump Inhibitors (PPI), have been reckoned as a magic solution and used vastly by physicians treating children with AR. Recent years have witnessed a surge in avant-garde pharmacotherapy in treating AR amongst children.[14] Yet, the results are hampered by the lack of in-depth understanding of the pathophysiology of AR in children. In this review, a summary of recent studies available on the association between NAR and AR in children will be discussed.

Methods

A PubMed, Embase, and Scopus database search was conducted for relevant peer-reviewed publications in the English language related to the respiratory manifestation of extra-esophageal reflux disease, AR amongst children. The following terms were used: ''gastroesophageal reflux''; ''gastroesophageal reflux disease'', ''silent reflux'', ''airway reflux'', ''acid reflux'', ''non-acid reflux'', ''children''. The literature search for the period January 2010 till November 2021 was conducted over a period of one-month: December 2021. The search terms were designed to incorporate all papers and therefore were intentionally broad. Following the initial search, the results were screened by title, then abstract, to identify papers meeting the inclusion criteria and to eliminate duplicates.

Selection criteria

The articles identified and selected were retrospective or prospective studies on children, published in the English language, that investigated, as a primary or secondary outcome, the relation between NAR and AR.

Full articles were then examined to ensure the selection criteria were met and were of sufficient quality to merit discussion. The search was conducted over a period of one month (December 2021). The review was conducted and reported with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[15] and Cochrane Handbook for Systematic Reviews of Interventions[16] when appropriate. Eleven original clinical research articles were selected based on our objective and selection criteria (Fig. 1).

Results

All studies included in this review revealed the presence of NAR as the main or secondary contributor in the development of AR amongst children. Of the total 11 selected studies, 6 are prospective studies, 3 retrospective studies, 1 cross-section study, and type of study was not mentioned in 1 study. Studies included in this review are summarized in Table 1.

Table 1 Summary of findings.

Name, Year	Type of study	Total	Mean age (years)	Gender	Respiratory manifestations	GI symptoms	MII-pH results	Additional investigations	Prior anti-reflux
Borelli et al.[2] 2010	Cross-sectional	21	4.1 (1.2–8.1)	9M/12F	Suspected pulmonary aspirations: 9 BA; 6 lung consolidation; 6 Recurrent croup	N/A	Total: 1505 reflux 736 (48.9%) NAR; 769 (51.1%) AcR; 1113 (74%) proximal	Fibreoptic bronchoscopy BAL LLM	NIL
Blondeau et al.[3] 2011	N/A	26	4 (1–10.5)	12M/14F	Chronic cough >8 weeks	Heartburn/ Abdominal pain/ Vomiting	Total: 967 reflux; 55.2% AcR; 41.5% WaC; 3.3% Walk; 26% Prox GER	Gastroesophageal manometry	NIL
Borelli et al.[4] 2011	Prospective	45	7.8 (1–16)	25M/19F	Chronic cough >4 weeks	N/A	CRR (Median); 86 reflux; 46 AcR; 12 Wac; 10 Walk; 43 Prox reflux	N/A	NIL
Ghezzi et al.[5] 2013	Retrospective	106	4.84 (2.76–8.16)	63M/43F	Chronic cough >8 weeks	Heartburn regurgitation, abdominal pain, vomiting	Total: 6623 reflux; 73.1% AcR; 26.9% Wac; 0 Walk	N/A	NIL
Rosen et al.[6] 2014	Prospective cross-sectional	112	76 months (13–200 months)	58M/54F	Cough 79% Croup 18%	N/A	Total: 48 reflux (med); 26 AcR; 22NAR; Prox 0.8%	Bronchoscopy& BAL Upper GI ensdocopy	NIL

Table 1 (*Continued*)

Name, Year	Type of study	Total	Mean age (years)	Gender	Respiratory manifestations	GI symptoms	MII-pH results	Additional investigations	Prior anti-reflux
Blasco-Alonso et al.[7] 2014	Prospective	39	3.52	25M/14F	ALTE	N/A	2692refluxes (83.6%); Reflux: 75; AcR 17(21.6); WaR 67.33; Other: 3.34; NAR 58	Laryngoscopy N/A	NIL
Dziekiewicz et al.[8] 2016	Prospective	18	1.7 (0.2–11.6)	15M/3F	Interstitial lung disease	12 neuroendocrine cell hyperplasia of infancy	1000 refluxes; 585 (58.5%) AcR; 407 (40.7%) WAR; 8 (0.8%) Walk; 637 (63.7%) Prox Ger	N/A	NIL
Pavic et al.[9] 2016	Retrospective	150	7.5 (0.3–18)	90M/60F	Chronic cough >8 weeks	Gastrointestinal symptoms in 32 (26.7%)	Reflux 42; AcR 14; Wac 23; Walk 0	Lung function test Radiological Immunological Allergy test	NIL
Zenzeri et al.[10] 2017	Prospective	40	58.3 (2–163 month)	20M/20F	Chronic cough: 82.5% Recurrent apnoe 7.5% Recurrent pneumonia 7.5%		Reflux 65.1 (Mean); AcR 40.8; WaC 2.2; Walk 22.1; Prox 57.9%		NIL
Pavic et al.[11] 2017	Prospective	104	8.9 (0.4–17.9)	57M/47F	LPR	N/A	Reflux 42; AcR 15.5; WAc 21; Alk 0; Prox 15	Endoscopy Eosinophil in nasal swab	NIL
Socso et al.[12] 2018	Retrospective	24	6.54	17M/7F	Recurrent LRTI Chronic cough Recurrent croup BA	Vomiting/ regurgitation	Median; AcR 37.5; Wac 16.5	Fibreoptic bronchoscopy BAL LLM	NIL

F, Female; M, Male; N/A, Data Not Available; AcR, Acidic Reflux; WaR, Weakly acidic Reflux; Walk, Weakly alkaline reflux; NAR, Non-Acidic Reflux; BAL, Bronchoalveolar Lavage; LLM, Lipid-Laden Macrophage.

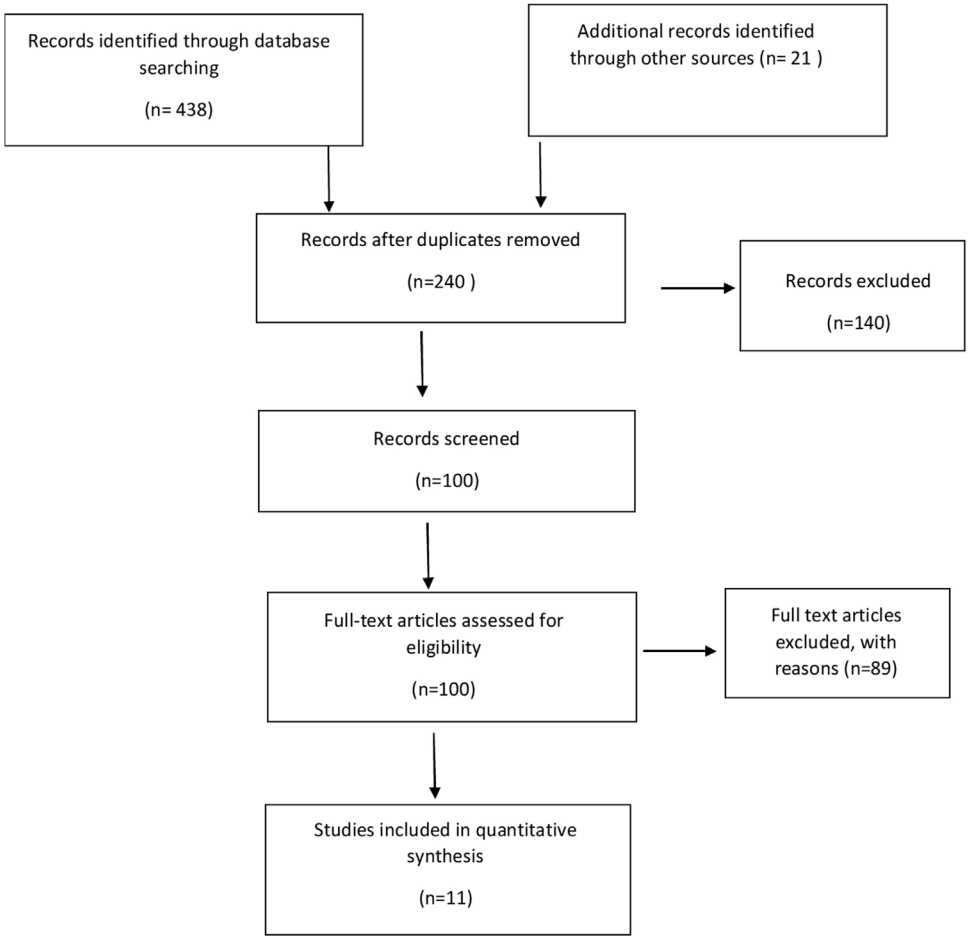

Figure 1 Flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for the systematic literature search.

The most common reported respiratory manifestation of NAR in children was chronic cough (7 studies), followed by other respiratory manifestations including ALTE, intractable asthma, croup, pneumonia, and interstitial lung disease. Predominant NAR was noted in 4 studies.[7,9,11,12] An overall male predominance was noted across most studies. The total number of children in each study ranges from 21 to 150 patients. The MII-pH study was carried out in all studies included as a diagnostic tool for reflux investigation. A 2-minute period following reflux onset was chosen to outline the time window for the association between cough and reflux during MII-pH. In 7 studies investigating association between cough and reflux, weakly alkaline reflux was the predominant NAR in 1 study,[10] whereas weakly acidic reflux was predominant NAR in 6 studies.

The additional adjunct investigation carried out in this review includes BAL (bronchoalveolar lavage),[1,6,12] fibre-optic bronchoscopy,[1,6,12] upper gastrointestinal endoscopy,[6] laryngoscopy,[4,6,9] lung function test,[4,9] radiological: chest radiograph,[4] chest and sinus computed tomography,[4] immunological,[6] allergy test,[6] eosinophil nasal swab.[11]

Discussion

The Discovery of NAR was an epiphany ensuing the dilemma faced by many physicians with intractable reflux manifestations in children despite religious usage of anti-reflux medication. NAR is a novel entity identified over the past century through the development of Multichannel Intraluminal Impedance with pH monitoring (MII-pH). NAR is defined when reflux from gastric content has a Ph > 4.0 using a threshold used by conventional pH monitoring, whereas when the gastric content shows Ph < 4.0, it is acid reflux. Additionally, when pH is >4.0 to 7.0, it is defined as weakly acid, whereas pH > 7.0 is termed as weakly alkaline.[17] NAR can be termed as postcibal reflux, as it occurs at the postprandial period following the rise in Transient Lower

Esophageal Sphincter Relaxation (TLESR) resulting from distension of gastric fundus post-meal. It is interesting that treatment with conventional anti-reflux medication such as proton pump inhibitors, despite altering the acidity of refluxate, fails to decrease the volume of reflux or affect the abnormal structure and motility of the gastroesophageal junction.

In children, numerous studies have associated preterm infants and NAR.[18,19] Children, especially infants, are postulated to have more NAR as NAR is associated with postprandial period when the refluxate are typically non-acid.[6]

Reflux manifestation of NAR is postulated to result from the stimulation of mechanoreceptors in the esophagus by the distension of the lower esophagus, the liquid-gas composition of NAR, as well as the extent of refluxate, which reaches proximal esophagus.[17,20,21] There are no specific symptoms attributed to NAR. NAR is suspected in cases of recalcitrant reflux symptoms despite maximal use of PPI.

The composition of gastric refluxate includes gastric acid, pepsin, conjugated bile salts, pancreatic enzymes, microbial pathogens, water, and the mixture of these components with food in the postprandial state. Traditionally acid, along with pepsin, was regarded as the main source of contributors of reflux-related diseases. However, observation of persistent reflux symptoms, albeit optimal anti-reflux treatment, has brought the revelation of NAR. Additionally, the advent of MII-pH, 'the new tool on the block', has shifted the paradigm in the management of reflux disorders. It is noteworthy that usage of anti-reflux medications, such as PPI, amongst children has resulted in more damage than before as acid refluxate are converted to non-acid refluxate. Apart from the composition of the refluxate, symptom perception, as well as mucosal damage, is related to the volume of refluxate and pattern of exposure.[22] It is known that a high proximal extent and a large volume of refluxate enables an individual to be aware of reflux events.[23]

Bile acids are considered a proinflammatory component of NAR. The myriad of *in vitro* and *in vivo* studies have demonstrated that bile acids possess toxic effects, especially to the laryngeal and tracheal tissue. Bile reflux is considered trivialized and has more detrimental effects on the airway epithelium and mucosa.

Another often trivialized component of NAR is gaseous refluxate. Gaseous refluxate are composed of either gas (belching) or combination of gas and liquid. More than 50% of refluxes are gaseous refluxate in resting-state.[24,25] The direct cause of mucosal injury of gas reflux remains questionable, yet, its role has been reported to contribute to reflux-related disease. The gaseous component increases the volume of the refluxate, thus leads to esophageal distension resulting in proximal refluxate.

Traditionally, pH probe has been used to diagnose gastroesophageal reflux and has been considered the 'gold standard'. It enables continuous monitoring of acid reflux for 24 h, thus increasing the probability of revealing if the presence of reflux symptoms correlates with reflux. However, a significant drawback of this tool is its inability to detect NAR.[6] Postprandial reflux, which is more prominent amongst children as they are continuously fed, becomes neutralized by stomach contents is overlooked when using pH probe as postprandial reflux is mostly NAR.[25,26] In keeping with that, children on anti-reflux have false-negative results due to the inability of pH probes to detect the NAR. pH correlation with reflux symptoms, especially in children, is still debatable.[27]

The Discovery of MII-pH has made it the crux in diagnosing reflux in children. MII-pH enables not only detection of acidic and nonacidic refluxate, but also able to differentiate antegrade from retrograde flow, measures the height of refluxate, determines the composition of refluxate whether it is liquid, gas or mixed as well as to assess symptom. Additionally, MII-pH study can be performed during numerous types of enteral feeding, including nasogastric, nasojejunal, bolus, and oral feeds.[19] The credibility of MII-pH is enhanced with the ability of patients to continuously take anti-reflux medication as it is pH-independent tool.[6]

Anti-reflux medications have been used vastly for treating both esophageal and extra-esophageal manifestation of reflux disease. Its role in curing extra-esophageal reflux disease in children has been contested lately. Recent years have witnessed a jarring increase in prescribing anti-reflux medications, notably PPI, for the treatment of extraoesophageal reflux.[28–30] PPI has been shown to be well-tolerated.[31] Hence, it has become the most favored anti-reflux medication. The dark side of anti-reflux medications, especially PPI has been trivialized. The increased use of PPI has been associated with an increased risk of respiratory infections in children, which worsens the patient's conditions instead of curing them.[32,33] PPI has been shown to increase susceptibility to acute gastroenteritis,[34,35] community-acquired pneumonia,[34,35] respiratory infections,[36] gastric polyp,[37] and bacterial overgrowth.[36] Interestingly, otorhinolaryngologists are currently the biggest prescriber of anti-reflux medication.[28]

Incidence and prevalence of various manifestations of airway reflux in children

AR entails respiratory manifestation of extra-esophageal reflux that has been reported by myriad studies[2–12] among children, which includes asthma, cough, laryngotracheal stenosis, laryngopharyngeal reflux, laryngitis, apnoe, Acute-Life Threatening Events (ALTE) and interstitial lung disease. Amongst children, postprandial reflux has been advocated as a physiological event that gradually disappears by one year of age, owing to the maturation of lower esophageal reflux and the ability to sit and stand.[38] Although reflux in children is considered physiological, recurrent contact of the refluxate on airway mucosa elicits various reflexes.[39]

Pathophysiology of AR entails comprehension of upper airway reflex triggered by reflux, notably Laryngeal Chemoreflex (LCR) which encompasses major cardiorespiratory control disorders resulting in recurrent apnoe of prematurity, ALTE, and SIDS. LCR is elicited upon laryngeal penetration of refluxate.[39]

Association between NAR and various AR

Reflux and cough

All studies investigating the association between cough and reflux reveal that cough is associated with reflux. During a

MII-pH, a 2-minute period following reflux onset was chosen to outline the time window for the association between cough and reflux. Cough is considered associated with reflux if it occurs within 2-minutes of reflux episode, and in case of cough occurs after the 2-minute window period, then it is considered to occur independent of reflux. Thus cough is not considered to be associated with reflux.[5] The study by Pavic 2016 involving 150 children revealed NAR, *i.e.* weakly acid reflux, to be the main cause of cough in their series.[9] Akin to that, several recent studies have shown NAR to be associated with cough amongst children.[3–6,9,10] Reflux characteristics based on the MII-pH study show median total number of refluxes: 48.7, and the mean number for NAR is 20.6. MII-pH was the pertinent tool that enabled identification of NAR as sole usage of pH probe will have missed the NAR component. Additionally, in all 7 studies included, weakly alkaline reflux was the predominant NAR in 1 study,[10] whereas weakly acidic reflux was predominant NAR in 6 studies.

Cough, when it takes place more than 4 weeks, are considered to be chronic. Chronic cough amongst children is a common presentation to the otolaryngology clinic. Albeit the numerous factors which may predispose to cough, gastroesophageal reflux has been attributed as one of the leading culprits. Reflux-related cough has been linked to three postulations; direct macro- or micro-aspirations by refluxate, recurrent refluxate, which leads to vagal irritation leading to tachykinin release,[40] or neural-cough reflex resulting from stimulation of oesophageal-bronchial system.[40,41] Diagnosing reflux-related cough amongst children remains a quandary amongst physicians as typical reflux symptoms such as regurgitation, vomiting, and heartburn are not present. Reflux-related cough patients state that cough occurs during the day, oftentimes in the upright position, triggered by phonation, eating, and upon rising from recumbent position.[42] Recent Cochrane meta-analysis involving both adults and children advocated that PPI therapy is not completely favourable.[43]

Reflux and laryngopharyngeal symptoms

A study by Pavic et al. revealed the association between NAR and laryngopharyngeal reflux.[11] Of the 104 children who underwent the MII-pH study, a median of 42 refluxes were obtained. A predominance of NAR was shown, whereby weakly acidic components resulted in a median of 21 refluxes, whereas acidic refluxes resulted in a median of 15.5 refluxes.

Reflux has been reiterated over the years to cause upper airway inflammation in children. A notable manifestation of this is Laryngopharyngeal Reflux (LPR). Endoscopic findings are pointing towards LPR, such as inter arytenoid edema and erythema, posterior glottic edema and vocal cord edema, and erythema.[44–48] 1 out of 5 children has been postulated to suffer from reflux.[49] Unsurprisingly, reflux in children has been linked with childhood obesity, whereby the rising incidence of childhood obesity has influenced numbers of reflux cases.[49] Among infants, the usual presentation of LPR includes regurgitation, vomiting, dysphagia, anorexia, failure to thrive, apnoe, recurrent croup, laryngomalacia, subglottic stenosis, or chronic respiratory issue.[49] Reflux finding score and reflux symptom index, which encompasses laryngeal symptoms as well as endoscopic findings, have been lauded to ameliorate findings amongst adults.[50] Yet, in children to date, there hasn't been any study to prove the effectiveness of both refluxes finding score as well as reflux symptom index.

Reflux and apnoe

Only 1 study in our review involved children with ALTE. None of the children had prior symptoms to suggest reflux. The MII-pH study was performed, which revealed an average of 75 refluxes with a predominance of NAR with 58 reflux episodes (73%) to 17 reflux episodes detected for acidic reflux. In this study, Blasco-Alonso et al. advocated on a combination of MII and pH study for accurate diagnosis as well as management.[7] It was revealed that pH-testing performed individually revealed a higher number of acidic reflux than MII as a small percentile of acid reflux events manifests as slow drops in pH are undetectable by impedance.

Apnoe in children has been linked with Acute Life-Threatening Events (ALTE) and Sudden Infant Death Syndrome (SIDS). The temporal association between reflux and apnoe has steered skepticism over the years. Various publications have reported reflux to be a prominent contributor of ALTE.[7,51,52]

Association between apnoe and reflux has been postulated to be around 20%.[7] Reflux and apnoe (either obstructive or mixed) have been reported to occur during waking hours, supine position or an hour after being fed.[7] Additionally, amongst preterm infants, apnoe of prematurity has been related with reflux, albeit the causal relation is not proven.[53] Stimulation of laryngeal afferents, which elicits central apnoe and laryngeal adduction, has been hypothesized to cause apnoe of prematurity.[53]

Another theory on how reflux leads to apnoe is explained by airway obstruction, which precedes laryngeal closure. Mucosal adhesive forces in animal studies have shown to play a critical role in maintaining upper airway patency. Mucosal inflammation secondary to reflux plays a huge role in aiding the collapse of the airway by increasing mucosal adhesive force.[54] Upper airway closure if accompanied by high surface mucosal forces, will foster further airway narrowing whilst impeding subsequent upper airway opening.[55]

Reflux and lower airway pathology

One study revealed an association between NAR and interstitial lung disease.[8] A cross-sectional study involving 18 children who had prior cough or dyspnoea. MII-pH study performed revealed 1000 refluxes, of which 58.5% were acidic, and 41.5% were NAR (40.7% weakly acidic; 0.8% alkaline reflux. GERD was diagnosed in 50% of patients, which showed a significant increase in proximal reflux (1.72 times) as well as total reflux (1.42 times).

Additionally, only 1 study involved described the association between NAR and pulmonary aspiration.[2] Children included in this study were diagnosed with bronchial asthma (9/21), lung consolidation (6/21), recurrent croup (6/21). The total number of refluxes amongst these children was 1505 refluxes, of which 48.9% were NAR. The number of

NAR was predominant in the children with lung consolidation compared to children with bronchial asthma and croup.

Numerous studies have reported on reflux being the main contributor of lung diseases such as pneumonia,[56] interstitial lung disease,[8] and recurrent croup[57] in children. Studies have shown GER to cause interstitial lung disease amongst adults ranging from 67% to 76%[58]; whereas in children, prevalence around 50% is noted. It is interesting to note that bronchial inflammatory reactions persist in patients treated with PPI,[59] which leads to suspicion of non-acid reflux to play a role in interstitial lung disease manifestation.[60] Savarino et al. reported that lung injury is greatly attributed to NAR as high levels of pepsin and bile acids were demonstrated from saliva and bronchoalveolar lavage fluid of patients with pulmonary disease.[60]

Reflux and recalcitrant asthma

Co-existence between asthma and reflux has been orated over the years.[61] This association was first observed by Sir William Osler in 1892, whereby worsening asthma was noted in a patient with distended stomach.[45] Contradictorily, this co-habitant has been considered a veridical paradox as asthma may cause reflux and vice-versa, yet treatment of reflux may not ameliorate asthma.[62] In adults, the prevalence of GERD symptoms in asthmatic patients is around 60%,[63] whilst in children, the numbers may reach a jarring 80%.[61] Albeit the countless hypothesis which exists till date on the mechanism of how GER causes asthma, the most notable ones includes[63,64]; 1) Aspiration theory: whereby microaspiration of gastric refluxate causes airway injury, 2) Reflex theory: stimulation of distal esophagus by gastric refluxate induces vagally-mediated bronchospasm and increased airway hyperresponsiveness, 3) Neurogenic theory: Gastric induced release of neurotransmitters such as substance P and neurokinin A into the airway, which causes airway edema, mucous secretion, vasodilation, and muscle contraction. GERD habitually manifests with heartburn and regurgitation; however, asymptomatic acid reflux in asthmatic patients has been shown to vary between 10% and 62%.[65] This warrants GERD investigation in all children with difficult to treat asthma.[66] Additionally, recalcitrant wheezing, asthma as well as airway hyperresponsiveness has shown significant susceptibility to develop heartburn and regurgitation symptoms.[62] Obese asthmatic children are more prone to develop GORD as compared to thin children.

Reflux and airway laryngotracheal stenosis

None of the studies in this review assessed the association between airway stenosis and reflux. Whilst exact pathophysiology behind airway stenosis remains a query, its association with reflux has been regarded as an axiom.[40] The postulated factor encompasses collagen-vascular disease, hormonal changes, occult trauma, and extra-esophageal reflux.[40] Both acid and non-acid reflux has been linked with upper airway stenosis.[40] Interestingly, reflux has been attributed to causing idiopathic Subglottic Stenosis (iSGS) in adults.[67,68] Earlier studies by Koffman et al. revealed reflux to be the main etiologic cause of upper airway pathology, by utilizing a 24-h dual pH-probe.[69] Animal studies revealed non-acid reflux, mainly pepsin, to induce airway stenosis,[70] which was supported by the study conducted by Blumin et al.[68] whereby biopsy of the stenotic scar in all patients which iSGS showed pepsin in the trachea and subglottic area. Amongst children, albeit iSGS is oftentimes associated with a developmental defect in cricoid cartilage, reflux has also been related to contribute if not the sole cause of Isgs.[68]

Implication for practise

Airway reflux is not a novel complication ensuing gastroesophageal reflux in children. Having said so, there is a lack of studies on presentations of various manifestations of AR as well as its pathophysiology amongst children. To date, the search for the ultimate elixir to curb reflux amongst children as well as adults remains undiscovered.

The existence of NAR has emerged following the vast implementation of MII-pH amongst children. NAR possesses humongous moiety in the development of AR in children. Knowledge on this entity is prudent as recently, over medication of anti-reflux has escalated across the globe. Unknowingly, attending physicians are worsening AR in children with continual usage of anti-reflux medication as the anti-reflux medication continues to pilfer the recovery process. Anti-reflux medication such as PPI especially has been reported to be associated with increased risk of respiratory infections, which may worsen the symptoms instead of treating them. The availability of MII-pH has improved our understanding of acid reflux and NAR. The importance of screening children with suspected AR with MII-pH cannot be emphasized more.

Conclusion

The elucidation of the relationship between NAR and AR in children holds the key to conquering this entity. The available evidence shows that there is strong evidence of the association between non-acid reflux and airway reflux in children. In our review, non-acid reflux was the predominant reflux to cause airway reflux in 4 studies. Further research on management in addition to long-term follow-up, will be valuable for in-depth understanding of this entity.

Conflicts of interest

The authors declare no have conflicts of interest.

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