

# **Gastroesophageal Reflux and Respiratory Diseases in Children linked:**

## **A Study Review**

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### **Introduction :**

Gastroesophageal Reflux Disease (GERD ) can be the contributing factor for many morbidities in the upper and lower Respiratory System, in this article I will connect GERD to each one of these morbidity and spot a light on a sometimes neglected diagnosis in the treatment that can if treated increase the chances of cure and decrease the need for surgery.

Gastro-Esophageal Reflux Disease in children First described as a pathological entity in 1950, with a predominance of 3:1 for males, The most common causes of occurrence of the gastroesophageal reflux in children are represented by: esophageal atresia, diaphragmatic hernias, prematurity (70% of newborns under 1700 g), gastrointestinal dyskinesias of different causes, feeding probes (for a long time). Other general causes include Lifestyle, obesity, poor posture (slouching), Medications — calcium channel blockers, theophyllines, antihistamines, Diet — Fatty and fried foods, chocolate, garlic and onions, acid foods such as citrus fruits and tomatoes, spicy foods, mint flavorings, Eating habits — Eating large meals or soon before bedtime, Other medical conditions — Hiatus hernia, diabetes, rapid weight gain. Also Children with neurodevelopmental disabilities, including cerebral palsy, Down syndrome, and other heritable syndromes associated with developmental delay, have an increased prevalence of gastroesophageal reflux.

Decreased gastric compliance is believed to lead to lower esophageal sphincter (LES) relaxation at lower intragastric volumes in infants. This aspect, in conjunction with abdominal wall muscle contraction as with crying (if it occurs during periods of LES relaxation) propels refluxate into the esophagus, with subsequent regurgitation reaching the upper and lower respiratory system (1).

GERD has been associated with general reactive airway complaints as otalgia, chronic nasal obstruction, headache, recurrent throat pain, hoarseness, stridor, chronic cough and respiratory stress.

These GERD related respiratory pathologies include:

- 1- Otitis Media and GERD:

Otitis media is one of the most high incidence illnesses during childhood , there have been several studies to link Otitis media (especially with effusion), to Gastroesophageal Reflux , these studies have collected middle ear effusions from children with Otitis Media and they found that these effusions were positive for anti-pepsin antibody , and Pepsinogens , the levels were around 1000 times higher than their levels in the serum, (middle ear Pepsin/pepsinogen levels ranged from 0.8 to 213.9  $\mu\text{g/mL}$  while serum reference levels 49.8–86.6  $\text{ng/mL}$ ) (2) (3) (4), which proves that the source of these secretions came directly from the stomach through the Eustachian tube. The pH of Middle Ear effusion samples was 7 to 9, and because of this (relatively high pH comparing to the gastric ph), only 29% of the Pepsin were active as this pH would inhibit pepsin activity, yet this activity was enough to participate in an inflammatory process in the middle ear, and to note also that (Pepsin) could be reactivated after a later decrease in Middle Ear pH in another episode of extra-esophageal reflux reaching the Middle Ear (5).

Other studies have found colonization of *Helicobacter pylori* in the Middle ear, tonsils, and adenoids, proven by PCR (Polymerase Chain Reaction) which indicates the presence of H-Pylory DNA, and also proven by culture of the Middle Ear fluids which proves the presence of live H-Pylory bacteria in the middle ear (6) (7), other systematic review of studies have found that *H. pylori* in the middle ear, tonsil and gastric juice was higher in children with Otitis Media with Effusion, while There is no clear connection between *H. pylori* detection in the Adenoids in children with Otitis Media with or without Effusion (8).

A Prospective Study of the Effect of GERD Disease Treatment on Children With Otitis Media found evidence that it significantly improve symptoms of Otitis Media in children (9) (10).

## **2- Sinusitis and GERD:**

Gasrtoesophagesl Reflux can cause inflammatory reaction in the upper respiratory tract as the mucosa there is not supposed to be in contact with acidic gastric secretions, the inflammation in the nasal region can cause edema of the mucosa and subsequent narrowing of the osteomeatal complex that guards the sinuses orifices, the result is obstruction of the normal sinuses secretions flow, leading to stasis of the mucus in the sinuses, bacterial growth, and resulting in Acute/Chronic Sinusitis. The other reaction to the acidic secretions is impaired mucocilliary clearance of the whole nasal mucosa, resulting in the stasis of the nasal secretions, crusting, and Chronic Rhinitis (11) (12) (13)

It is still debatable that GERD can cause Acute and Chronic Rhinosinusitis in children but several studies have found marked improvement in the symptom of the nose and the sinuses after successful treatment of GERD in children (11) (14) (16). Bothwel and his colleagues found that the indication for surgery for the treatment of CSD ( Chronic Sinus Disease ) in children was much less after the treatment of GERD (15). This is very

important as the nasal surgery in children has limited results, not to forget the potential risks of this surgery and the possible effects on facial growth, which prompt us to try every conservative medical treatment option before opting for surgery. It is also important to eliminate all contributing factors of CSD including GERD, to decrease the need for the use of antibiotic and cortisone in children. (17)

### **3- Enlarged Tonsils, Adenoids and GERD:**

It was found that there was high prevalence of enlargement of Adenoids and Tonsils in children with GERD, although the mechanism is not completely proven but it is expected that Pepsin and the acidic Gastric juice has an inflammatory effect on the lymphoid tissue of Adenoids and Tonsils, besides the colonization of H. Pylori bacteria in the lymphoid tissue of the upper respiratory tract and the immunological response in these tissues.

In a meta-analysis of six studies with a total sample size of 548 cases there was an effective evidence for the relation between GERD and Enlarged Adenoids (18), the children with adenoid hypertrophy had a higher incidence of GERD than healthy children, but the pathogenesis of GERD in adenoid hypertrophy awaits more investigations and suggests that we should not overlook GERD in the evaluation of enlarged Adenoids.

There are reports that pepsin was detected in upper airway mucosa especially around tonsillar clefts and in the damaged tonsil squamous epithelium, inducing a pro-inflammatory reaction mediated by macrophage and cytokine cycle, an immunological reaction that can be related to the tonsillar enlargement (19).

One study used Pepstatine ( which inhibits Pepsin activity ), and studied the inflammatory mediators in specimens from the enlarged tonsils, and found reduction in these mediators after the use of Pepstatine, that means Pepstatin suppressed Pepsin-mediated lymphocyte proliferation in tonsil hypertrophy (20) , a systematic review suggests an association between Lingual Tonsil Hypertrophy (LTH) and reflux in both adults and children. (21).

By understanding the histopathologic process underlying the tonsillar hypertrophy and maybe other lymphoid tissues like adenoids we can reduce the need for surgery in children whom GERD might be a causative factor for their enlarged Adenoids and Tonsils.

### **4- Laryngeal, Pulmonary manifestations and GERD:**

Many manifestations can be found in the Supralaryngeal, Laryngeal, and Tracheal regions as a result to the Gastroesophageal Reflux, this could include: Acute Recurrent and Chronic Laryngitis and the resulting Chronic Hoariness, Sore throat, Persistent Coughing, Paroxysmal laryngospasm, Bronchospasm, recurrent Pneumonitis. (1)

The changes in this region associated with GERD can be observed by Laryngo-Broncho Scopy (LBS) using the fixable Laryngo-Tracheal Scope, as we could see

Laryngomalacia, Supraglottic and glottic edema and Stenosis, Aretenoid edema, laryngo-tracheal stenosis, increased tracheal secretions. (22) (23) (24) (25)

Gastric enzymes and the very low pH Gastric secretions are very irritating to the Pharyngeal, Laryngeal, and Tracheal mucosa, this irritation causes inflammation, granulation tissue, and edema in these regions, knowing that it is difficult to distinguish between aspiration from the stomach and aspirated food during children feeding.

We must note that the absence of these finding does not rule out GERD if the reflux is limited to the Esophagus and does not reach the Laryngeal level, yet Esophageal irritation can be the cause of reflective neurally mediated lower respiratory symptoms, such as hiccups, laryngospasm, bronchospasm, central apnea, and bradycardia.(1) (24)

These finding have been found to be associating GERD children patients with a statically high enough index to be considered as mandatory to evaluate in all GERD children that have syndromes as the ones mentioned above. In a study Matthews et al reported the presence of pharyngeal acid reflux in all of a group of 24 children with laryngomalacia, in all these children there was Laryngeal Edema and proved acid reflux to the Pharyngeal level. (26)

Studies are needed to correlate GERD treatment to healing effect on the Laryngeal and Tracheal mucosa.

#### **5- Asthma and GERD:**

There is a both way interaction between Asthma and GERD, that's why nearly half the number of children with Asthma has GERD. (27)

Most of asthmatic children have GERD and it is a well-documented fact that GERD plays an important role in patients with asthma. It is still difficult to define Asthma children patients that will respond well to anti reflux therapy, as it is difficult to establish the cause-and-effect relationship between asthma and GERD. (28 ) (29)

A study reported that obese children had seven times higher odds of reporting multiple GERD symptoms and that asthma symptoms were closely associated with gastroesophageal reflux symptom scores in obese patients but not in lean ones. (30)

**Asthma can cause GERD** by decreasing the intrathoracic pressure during the inspiration, and the relative higher intra-abdominal pressure during the coughing episodes, this causes a difference of pressure that can lead to acid reflux into the esophagus and the pharynx. There is also the side effect of some Asthma medications like Nebulized Albuterol (31), theophylline (32) that can relax the lower Esophageal sphincter ( LES ), causing Gastroesophageal reflux.

On the other hand **GERD can cause Asthma** by the irritation to the Esophagus and a neural reflex mediated by the Vagus Nerve can cause spasm of the Bronchuses with resultant cough, and increased mucus secretion from the respiratory mucosa. Also there is another possible mechanism by bronchial aspiration of the Gastric refluxed secretions,

which is very irritating to the bronchial and laryngeal mucosa causing the inflammatory reaction including increased secretions, bronchial spasm, and cough (1)

GERD must always be in mind when treating asthmatic children especially the very young ones as their digestive system may not be well developed to prevent the reflux, causing repeated cough and other respiratory syndromes, and also their airway is small that any decreasing in its diameter by the mucosa swelling or bronchospasm can cause severe breathing difficulty. (33)

#### **6- Juvenile Recurrent Respiratory Papillomatosis ( JRRP ) and GERD:**

Recurrent respiratory papillomatosis (RRP), which is caused by human papillomavirus types 6 and 11, is the most common benign neoplasm of the larynx among children, although histologically benign, it is so difficult to control and can cause severe morbidity and mortality. Symptoms include changes in voice, stridor first inspiratory and then biphasic, chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, or acute respiratory distress, especially in infants with an upper respiratory tract infection.

There is no direct proven link between JRRP and GERD, but it is believed that the irritation caused by the refluxed acid can re-activate the latent Human Papilloma Virus (HPV), causing the re-eruption of the papilloma in the Larynx and Trachea (34). One study found that nearly 45% of children age between 4 and 14 years old with diagnosed JRRP had pathologic Gastro-Esophageal Reflux proven by the presence of Pepsine in the cytoplasm of the Laryngeal papilloma tissues extracted during surgery for the treatment of JRRP, although there could not be proof that GERD can be a cause of JRRP in this small group of children. (35)

Prompt diagnosis and effective treatment of GERD should be considered in all patients with difficult to control JRRP. (36) (37)

Case studies have shown that treating gastroesophageal reflux disease (GERD) with anti-reflux medication in patients with juvenile-onset RRP can help slow the rate of papilloma regrowth, and patients who failed to comply with GERD treatment experienced recurrence. (38) (39) (40)

#### **Summery**

Gastro-Esophageal Reflux Disease can be the cause for multiple illnesses and pathologies in the Upper and Lower respiratory tract System of children. GERD is usually a missed diagnosis during the context of these other illnesses, it's treatment is essential for the successful management of these medical conditions that can shorten the period of treatment, decrease or even eliminate the need for surgery in some cases.

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