INTRODUCTION

Gastroesophageal reflux disease (GERD) is the condition that results when gastric material that refluxes into the esophagus or oropharynx causes symptoms, tissue injury, or both ***(Spechler, 2000)***.

Gastroesophageal reflux is a common problem that occurs in the pediatric population. The prevalence of GER in young infants, although difficult to ascertain, because most infants are not brought to medical attention, can be estimated between 1% and 10%. As for the natural history of GER, it must be emphasized that reflux disappears spontaneously within the first 18 months of life in 80% of cases, with or without conservative therapy. It can persist until 24 months in 15% of infants, and in 5% it does not resolve and transforms into GERD ***(Cavataio et al., 2000)***.

GER is a normal physiological process occurring daily in healthy infants with similar frequency in both breast- and bottle-fed infants. In contrast, GERD is associated with more severe symptoms and, on occasions, oesophagitis ***(Falconer, 2010)***. Also GERD can be associated with other manifestations such as: failure to thrive, weight loss, feeding or sleeping problems, chronic respiratory disorders, hematemesis, stricture, sideropenic anemia, apnea, apparent life-threatening episodes or sudden

infant death syndrome, and Sandifer's syndrome***(Salvatore and Vandenplas, 2002)*.**

GERD may be primary or secondary,secondary GERD is associated with a number of genetic syndromes, chromosomal abnormalities, birth defects, hypertrophic pyloric stenosis, gastric or duodenal ulcer, annular pancreas***(Henry, 2004)***. And also can be caused by infections, metabolic disorders, and food allergy***(Salvatore and Vandenplas, 2002)***.

CMPA is one of the recognized causes of 2ry GERD ***(Magazzu, 2002)***. The prevalence of cow's milk protein allergy (CMPA) is estimated to be between 2% and 3% in infants and marginally lower in older children ***(Kneepkens and Meijer, 2009)***. The relation between these 2 entities has been investigated and some important conclusions have been reached: in up to half of the cases of GERD in infants younger than 1 year there may be an association with CMPA. In a high proportion of cases GER is not only CMPA associated but also CMPA induced ***(Salvatore and Vandenplas, 2002)***.

The diagnosis of GERD in children is made based upon the child's history and data derived primarily from pH monitoring tests and endoscopy ***(Gold and Freston, 2002)***. Management of GERD begins with a nonpharmacologic approach; the emphasis is on positioning and thickening of

feedings. When these measures fail to control symptoms, a trial of either histamine (2) receptor antagonists or a proton pump inhibitor may be indicated. Finally surgical treatment may be needed if all other management measures fail ***(Henry, 2004)***.

Proton Pump Inhibitors (PPIs) are the most effective pharmacologic agents available for the treatment of children with GERD. In the pediatric practice only omeprazole, lansoprazole and esomeprazole are available over the first year of life. The empiric use in infants with nonspecific symptoms (excessive crying, regurgitation, feeding refusal, chronic cough) is frequent ***(Romano et al., 2011)***.

CMPA results from an immunologic reaction to one or more milk proteins. Early diagnosis and adequate treatment decrease the risk of impaired growth. CMPA can develop in exclusively and partially breast-fed infants, and when CMP is introduced into the feeding regimen. CMPA persist in only minority of the children. The prognosis depends on the patient's age and titre of specific IgE at the time of diagnosis. ***(Vandenplas et al., 2007).*** At present, the only proven treatment consists of elimination of cow's milk protein from the child's diet and the introduction of formulas based on extensively hydrolysed whey protein or casein; amino acid-based formula is rarely indicated. The majority of children will regain tolerance to cow's milk within the first 5years of life***(Kneepkens and Meijer, 2009).***

HYPOTHESIS& AIM OF THE WORK

The aim of this work was to compare the efficacy of elimination diet versus elimination diet with addition of a proton pump inhibitor in the treatment of Cow's milk protein allergy related Gastro-esophageal reflux disease.

PEDIATRIC GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux (GER) is the effortless passage of gastric contents into the esophagus. It can consist of gas (eructation, or burp) or fluid (possiting, wet burp, "spitting up" in infants, or, incorrectly, vomiting). In normal children and adults, this occurs several too many times a day, but fluid rarely reaches the mouth ***(Jones, 2001).***

Pediatricians usually diagnose many infants who have effortless, painless regurgitation, mainly following feeding. These young children usually grow well and their regurgitation tends to stop by six months of age. This is known as functional (non pathogenic) GER ***(Orenstein et al., 1999).***

GER is a prevalent gastro intestinal (GI) problem in pediatrics. Many infants have recurrent problems of spitting up and vomiting during the first year of life. The gastric contents can vary and includes saliva, ingested foods, gastric, pancreatic, or biliary secretions.Regurgitation is the passage of refluxed gastric contents into the oralpharynx ***(Vandenplas, 2000).*** The term regurgitation is used if the reflux dribbleseffortlessly into or out of the mouth and is restricted to infancy (from birthto 12 months) ***(Vandenplas and Hegar, 2000).***

GER occurs when gastric contents move into the esophagus as the result of transient relaxations of the lower esophageal sphincter (LES), an abrupt decrease in LES pressure to the level of intragastric pressure unrelated to swallowing, or when the LES tone does not compensate for changes in abdominal pressure ***(Mittal et al., 1995).***

The distinction between functional GER and pathogenic GERD lies in the demonstration of abnormal frequency or severity of the reflux or the presence of complications such as failure to thrive or weight loss, feeding or sleeping problems, chronic respiratory disorders, esophagitis, hematemesis, esophageal stricture, iron deffiency anemia or apparent life threatening episodes and Sandifer's syndrome ***(Orenstein, 2000).***

Epidemiology

GERD is one of the commonest GI complaints in infancy; the incidence of the condition is reported to be 20% to 40% in infants***(Keady, 2007).***

The prevalence of GER varies according to age, particularly in children. Daily regurgitation is present in 50% of infants younger than 3 months, in >66% at 4 months, and in 5% at the age of 1 year. Complete resolution of regurgitation occurs by 10 months in 55%, by 18 months in 60% to 80%, and by 2 years in 98%. Determination of the prevalence of GERD at any age is difficult because of increasing self-treatment and lack of

medical referral. Children with GERD have esophagitis in 15% to 62%, with Barrett esophagus in 0.1% to 3%, and with refractory GERD requiring surgery in 6% to 13% ***(Hoffman et al., 2010)***.

Etiology of GERD

GERD may be primary or secondary to other conditions***(Magazzu and Scoglio, 2002).***

Primary GERD

Primary GERD results from dysfunction of the esophagogastric junction ***(Norton and Penna, 2000).***

Secondary GERD

Secondary GERD may be associated with, tracheoesophageal fistula, deglutition disorders, hypertrophic pyloric stenosis, gastric or duodenal ulcer, annular pancreas, intestinal pseudoobstruction, CMPA, urinary infection, intestinal parasitoses, genetic-metabolic diseases, asthma, cystic fibrosis ***(Norton and Penna, 2000).***

The relation between H. pylori and GERD is controversial, H. pylori infection was positively associated with reflux esophagitis (RE) thus H. pylori appeared to be a risk factor for this biomarker of GERD ***(Moon et al., 2009).*** The type of infant formula may also contribute to reflux. In a small group of infants being assessed for reflux, high osmolality feedings significantly worsened reflux ***(Faubion and Zein, 1998).***

Motility disorders are postulated to potentially cause reflux since an association between diminished LES tone, transient lower esophageal sphincter relaxation (TLESR), delayed gastric emptying and GER have been recognized ***(Indrio et al., 2009).***

Pathophysiology

GER is the retrograde movement of gastric contents into the esophagus***(Taminiau, 1997).*** It is a normal physiologic process that occurs in every one, particularly after eating***(Marc Tsou and Bishop, 1998).*** GERD in infants occurs when the esophageal mucosa is damaged by excessive exposure of the distal esophagus to gastric contents ***(Boyle et al., 1989).***

CMPA is one of the recognized causes of secondary GERD***(Magazzu and Scoglio, 2002).*** About 40% of infants referred for specialist management of GERD have allergy to CMP. These allergic reactions are frequently not IgE mediated ***(Kemp et al., 2008).*** An association of CMPA and severe GERD was observed not only in infants but also in preschool/school children ***(Nielsen et al., 2004).*** It has been suggested that infants with GER should be evaluated for allergy to CMPA***(Salvatore and Vandenplas, 2002).*** Figure (1) shows interactions between CMPA, Esinophilic esophagitis (EE) and GERD. Each entity may exist alone, although overlapping states exist as CM sensitive GERD and allergic eosinophilic oesophagitis. Pure GERD is characterised by increased oesophageal acid exposure and minimal eosinophilic infiltration

in oesophageal biopsies, whereas the opposite is seen in eosinophilic oesophagitis ***(Nielsen et al., 2006).***

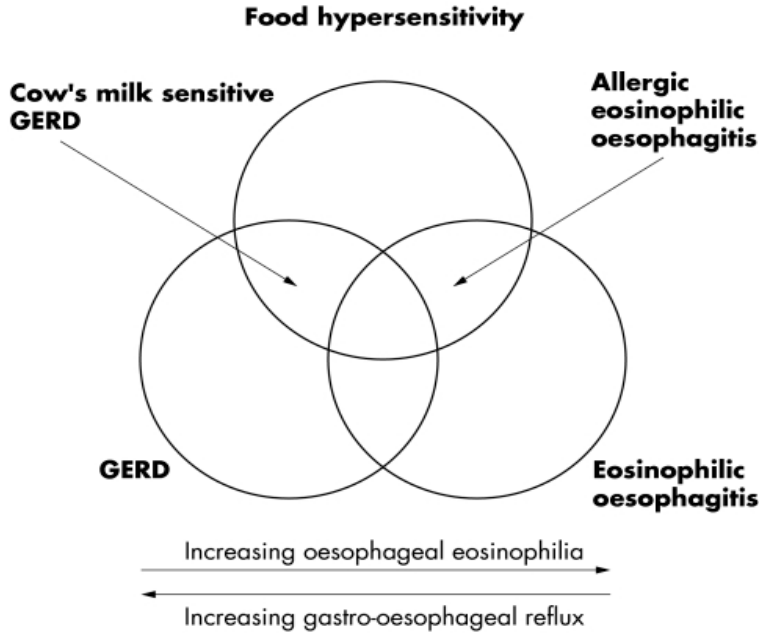

Figure (1): Interactions between gastro–oesophageal reflux, food hypersensitivity, and eosinophilic oesophagitis ***(Nielsen et al., 2006)***.

I. Esophageal Disorders:

A- Transient Lower Esophageal Sphincter relaxation (TLESR):

It is recognized that the LES creates a high pressure zone between the esophagus and the stomach that prevents reflux. An effective LES must have an adequate total and intra-abdominal length, and an adequate resting pressure***(Zaninotto et al., 1988).***TLESR was supposed to be the most common mechanism leading to GER. During TLESR, both the LES and the crural diaphragm are inhibited for 10-60 seconds, and this

inhibition is mediated by a brainstem reflex ***(Zeiter and Hyams, 1999).*** A normal LES pressure does not exclude GERD, because abnormal transient relaxation might occur ***(Kahrilas, 1997; Patti et al., 1997).***However in infants and children, TLESR is responsible for only 50% of reflux episodes***(Marc-Tsou and Bishop, 1998).***

It has been shown that a mechanically incompetent LES is progressively associated with worse mucosal damage ***(Meneghetti et al., 2005).***

B- Peristaltic Dysfunction and Impaired Esophageal Clearance:

Esophageal peristalsis is an important component of the antireflux mechanisms because it is the main determinant of esophageal clearance of the refluxate. Defective peristalsis is associated with severe GERD, both in terms of symptoms and of mucosal damage. It is known that 40-50% of patients with GERD have abnormal peristalsis ***(Diener et al., 2001).*** This dysmotility is particularly severe in about 20% of patients because of very low amplitude of peristalsis and/or abnormal propagation of the peristaltic waves (ineffective esophageal motility)***(Patti and Perretta, 2003).***

Esophageal clearance is slower than normal, therefore, the refluxate is in contact with the esophageal mucosa for a longer period of time and it is able to reach more often the

upper esophagus and pharynx. Thus, these patients are prone to severe mucosal injury (including Barrett's esophagus) and frequent extra-esophageal symptoms such as cough ***(Patti and Perretta, 2003; Meneghetti et al., 2005).***

II. Transient and Sustained Increase Intra-abdominal Pressure:

Permanent increase of the intra-abdominal pressure (obesity) or its transitory increase (deep inspiration, coughing, physical exercises, Valsalva manoeuvre, constipation and others), are factors that predispose to reflux***(Norton and Penna, 2000).*** It has been shown that patients with end-stage lung disease have a high prevalence of GERD; up to 70% ***(Sweet et al., 2006).***

III. Delayed Gastric Emptying:

Abnormal gastric emptying may contribute to GERD by increasing intra-gastric pressure ***(Mariani et al., 2004).*** Delayed gastric emptying has been found in young children with GERD complicated by failure to thrive and respiratory symptoms***(Boyle et al., 1989).***

Delayed gastric emptying is present in 10% to 15% of patients with GERD. It is believed to contribute to the development of a small proportion of cases by increasing the amount of fluid available for reflux and by the associated constant gastric distention. Potential causes of impaired gastric

emptying include gastroparesis, as seen in patients with diabetes, and partial gastric outlet obstruction ***(Kahrilas, 2003).***

IV. Acidity of Gastric Secretions (Aggressive Refluxate):

Gastric and duodenal contents can reflux into the esophagus. Gastric hydrochloric acid has long been recognized as harmful to the esophagus ***(Herbella et al., 2009).*** However, gastro-esophageal refluxate contains a variety of other noxious agents, including pepsin ***(Tacket al., 2004).***

V. Dudenogatroesophageal Reflux (alkaline reflux)

Reflux of duodenal juice in GERD is more common than pH studies alone would suggest. The combined reflux of gastric and duodenal juices causes severe esophageal mucosal damage. The vast majority of duodenal reflux occurs at a pH range of 4 to 7, at which bile acids, the major component of duodenal juice, are capable of damaging the esophageal mucosa ***(Kauer et al., 1995).***

Clinical presentation

GERD can present in typical or atypical fashion. Typical symptoms of GERD include heart burn, vomiting, regurgitation, sore throat, and a sour or bitter taste in the month commonly referred to as water brash. In infants and young children, the physician must recognize non verbal clues, such as crying, irritability, sleep disturbances, poor appetite, and weight

loss, as signs of GERD ***(Dellert et al., 1993).*** Atypical manifestations of GERD include apnea, bradycardia, wheezing, stridor, recurrent pneumonia, chronic cough, Sandifer's syndrome, and laryngitis ***(Scott et al., 1999).***

Presenting features of GERD in infants and children are quite variable and follow patterns of GI and extra-intestinal manifestations that may vary according to age. **Table** (1) lists the variable manifestations of GERD.

Table (1): List of variable manifestations of GERD

Gastrointestinal system	**extra-intestinal manifestations**
_ Vomiting, regurgitation, rumination _ Failure to thrive, malnutrition _ Gagging _ Esophagitis _ Peptic stricture _ Barrett's esophagus _ Anorexia, feeding refusal _ Apparent life-threatening event _ Sandifer's syndrome (GER with torticollis) _ Dysphagia, hypersalivation _ Arching _ Abdominal and epigastric pain, heartburn, sleep disturbances dental erosion -- Ulcerative esophagitis	_ Reactive airway disease _ Apnea _ Cough and choking _ Aspiration pneumonia _ Bronchopulmonary dysplasia _ Bronchitis _ Stridor _ Hoarseness _ Subglottic stenosis _ Laryngospasm _ Sudden infant death syndrome _ Recurrent wheezing _ Chronic laryngitis, _ Asthma _ Chest pain _ Irritability, excessive crying _ Anemia, bleeding _ Bradycardia _ Sleep disturbances

(Sunku et al., 2000; Monzani and Oderda, 2010)

In some children, bronchospasm may be the only manifestation of the reflux (occult GER) ***(Norton and Penna, 2000).***

ENT manifestations of GERD mainly affect the larynx, ears, nose, paranasal sinuses and oral cavity. Main manifestations are laryngo-tracheal stenosis,laryngomalacia, otitis media with effusion, rhinosinusitis ***(Caruso and Passali, 2006).***

Diagnostic Evaluation:

The diagnosis of GER can be made in most cases based upon the history and physical examination. Therapy with conservative measures and, if indicated, medications can be initiated empirically ***(Vandenplds et al., 1993).***However, if the presentation is atypical or if the response to treatment is suboptimal, evaluation beginning with an upper gastrointestinal series (UGI) is warranted ***(Vandenplas et al., 1997).***

I. Imaging Studies:

A) Upper Gastrointestinal Imaging Series:

The UGI is useful to delineate the anatomy of the upper GI tract ***(Johnston et al., 1996).***The UGI also can demonstrate functional aspects such as deglutition and esophageal motility ***(Kahrilas and Gupta, 1990).*** The sensitivity, specificity and positive predictive value of the upper GI series range from 31% to 86%, 21% to 83%, and 80% to 82% respectively when compared to esophageal pH monitoring ***(Rudolph et al., 2001).***

B) Ultrasonography

Conventional ultrasonography have reported to be a reliable non invasive method to detect reflux events and as well to describe anatomical conditions such as hiatal hernia, length

and position of the LES and the magnitude of the gastro-esophageal angle of His. Dynamic ultrasound may be useful for the study of the gastric emptying time ***(Chuah et al., 2009).***

C)Scintigraphy

This is done by adding a known quantity of Tc99m sulfur colloid to food (solid and/or liquid) and then placing the patient under a gamma counter in order to calculate how rapidly the isotope leaves the stomach ***(Hassall et al, 1992).***The areas of interest (the stomach, esophagus and lungs) are scanned for evidence of GER and aspiration. Unlike esophageal pH monitoring, the nuclear scan can demonstrate reflux of non-acidic gastric contents. Scintigraphy also provides information about gastric emptying, which may be delayed in children with GERD.Episodes of aspiration may be detected during a one-hour study or on images obtained up to 24 hours after the feeding is administered.The reported sensitivity and specificity of the nuclear scan for the diagnosis of GER are 15% to 59% and 83% to 100%, respectively, when compared to esophageal pH monitoring ***(Rudolph et al., 2001).***

II.Procedures:

A) Esophagogastroduodenoscopy (EGD):

Endoscopy associated with histology is a reliable and accurate method to demonstrate esophageal damage induced by GERD, such as inflammation and strictures ***(El-Serag et al., 2002).***