Gastro-oesophageal Reflux and Cow's Milk Allergy

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Abstract

Gastro-esophageal reflux disease (GERD) and cow's milk allergy protein (CMPA) and are both common disorders in childhood, mainly infancy, and several studies have hypothesised a causal relationship between them, suggesting that at least in a subgroup of infants GERD is attributable to CMA. In children with CMPA, a neuroimmune interactions provoked by cow's milk challenge might induce gastric motor abnormalities and in turn increase the number of reflux episodes. Studies assessing the relationship between the two conditions have shown an association ranging between 16 and 55%, which is far beyond from that expected from pure coexistence. Therefore, a possible concomitant CMPA, mainly in those infants and children with GERD unresponsive to medical treatment data, should be highly considered. Current ESPGHAN-NASPGHAN guidelines already suggest a short trial cow's milk free diet in those infants with chronic regurgitation unresponsive to medical therapy, vomiting and failure to thrive.

Keywords

Gastroesophageal reflux • Cow's milk protein allergy • pHmetry • pH-impedance

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Introduction

Allergy is an immune-mediated disorder involving all tissues and organs where immune cells might dwell. Historically, immune-mediated reactions have been distinguished in four major types according to the first classification provided by Coombs and Gell [1]. For the purpose of our chapter, it is only important to mention that allergic reactions can either be immediate, implying an IgE-mediated reaction, or delayed, which are not IgE mediated.

Gastrointestinal (GI) allergies are almost generally mentioned and simplified as "food allergies", since food antigens are the culprits in deranging the physiologic gut immune response in genetically susceptible individuals. However, it is worth mentioning that some foods might cause adverse reaction for immunological, chemical and pseudo-pharmacodynamic interactions, such as in coeliac disease, non-coeliac wheat sensitivity and scombroid fish poisoning.

Allergy-related clinical conditions such as food allergy, rhinitis and eczema have witnessed a constant rise over the last decades, and this trend has not changed [2, 3].

Food allergy prevalence is estimated to be roughly 6–8% in paediatric group. The prevalence is highest in infants and toddlers, with 2.5% of infants suffering from milk allergy and up to 10% of children older than1 year suffering from food allergies, such as cow's milk, egg, nuts, soya, wheat and fish/shellfish [4]. It should be noted that prevalence data are often derived from studies in western populations, which focus on a relatively limited number of foods [5]. Districting patterns of food consumption and allergic sensitization might bias the relevance of specific foods to the public health in different countries [6].

Cow's milk protein allergy (CMPA) is the most common food allergy in infants with prevalence in early childhood of approximately 2–3% in developed countries [7]. CMPA has been identified as a worldwide health problem with high costs and burden for little patients and their families [8, 9]. CMPA has been frequently identified as the underlying cause in common gastrointestinal motility disorders of the childhood such as gastro-oesophageal reflux disease (GORD), recurrent abdominal pain, diarrhoea and constipation. The definitive diagnosis of allergy in these conditions, however, is difficult since CMPA could be non-IgE mediated and thus confirmed only by means of exclusion diet trial and subsequent re-challenge.

This chapter aims to review the putative mechanisms for allergy in GORD and to provide a comprehensive snapshot of available evidence on the topic.

Pathophysiology

In the eighties a clinical study showed that an enteropathy with abundant IgE plasmocytes as well as a rise of intraepithelial lymphocytes could be found in children with GORD attributable to CMPA [10]. The mechanisms by which food allergy causes gastrointestinal motor abnormalities are still a matter of debate. However, it is widely shown that allergic reactions to food proteins, either due to non-IgE or IgE-mediated mechanisms, induce mucosal infiltration and activation of different

type of inflammatory cells, such as eosinophils, mast cells (MCs) and B and T lymphocytes, throughout the gastrointestinal tract [11]. Eosinophils and MCs are considered the key effector cells of both immediate and delayed-type hypersensitivity reactions, and upon activation they release a variety of pro-inflammatory, nociceptive and vasoactive mediators as well as significant number of neurotransmitters. Within the gastrointestinal tract, MCs are in close apposition to nerve endings, and therefore their activation and degranulation are able to evoke different neuromuscular responses, such as activation of muscle contractility and neural reflexes, which might ultimately result in change gastrointestinal motor functions [12, 13].

Several studies in experimental animal models of food hypersensitivity have shown that antigen challenge in vivo is able to induce panenteric motor abnormalities, such as delayed gastric emptying, altered gastric secretion and disruption of both preprandial and postprandial small intestine motor activity with small intestine disappearance of cyclic MMC during fasting period and inability in activating the fed motor activity [14–16]. Moreover, the motor abnormalities induced by antigen challenge parallel the histological evidence of mast cell degranulation in the gastric mucosa as well as the increase in both specific markers for mucosal MC degranulation and intraluminal release of histamine and persist long after the initial challenge [17].

In children, early-onset neuroimmune interactions induced by cow's milk challenge in the gastric mucosa of atopic children could cause prompt imbalance of gastric myoelectrical activity. Ravelli et al. showed that in infants with vomiting induced by CMPA, milk challenge induces delayed gastric emptying and gastric myoelectrical dysrhythmias [18]. Few years later, Schaeppi and coworkers confirm the previous data showing that early-onset neuroimmune interactions induced by cow's milk challenge in the gastric mucosa of atopic children parallel the rapid derangement of gastric myoelectrical activity [19]. Notably, cow's milk exposure of the gastric mucosa induced a rapid degranulation of MCs and eosinophils. Activated MCs migrated in proximity of mucosal nerve fibres; moreover tryptase released from MCs was colocalized with proteinase-activated receptors 2 (PAR-2) on the same fibres. In the interim, there was a swift induction of electrogastrographic myoelectrical abnormalities. Intriguingly in the stomach of animal models, PAR-2 induces neurally mediated motor and secretory response, more specifically a fundic biphasic contractile response which implies relaxation followed by contraction [20]; in addition, a suppression of acid production follows this activity mediated by PAR-2 [21].

Furthermore, it has been identified that episodes of dysrhythmia are possible causes of antral hypo-contractility, which in turn promotes a delay of stomach emptying [22]. A delay in gastric emptying might increase gastro-oesophageal reflux by increasing the availability of material to reflux or by inducing prolonged gastric distention and by increasing the frequency of transient lower oesophageal sphincter relaxations (TLOSRs), which are the main underlying mechanism of gastro-oesophageal reflux [23]. It could be speculated that in a subgroup of infants and children with CMPA neuroimmune activation evoked during milk challenge might derange the gastric motor activity and hence delay the gastric emptying and increase the rate of TLOSRs, resulting in an increase in the number of reflux episodes.

Clinical Picture and Diagnostic Strategies

It is clear that allergy to cow's milk protein may cause symptoms such as irritability, distress and vomiting indistinguishable from GORD, thus complicating the diagnostic pathway in the clinical practice.

Although most studies report a comparable incidence of regurgitation in unselected populations of formula versus breastfed infants, Hegar et al. reported a higher incidence of regurgitation in formula-fed infants [24]. Alongside this consideration, it should be stressed that the prevalence of CMPA is five to ten times higher in formula fed than in breastfed infants [25], thus fashioning the possible epidemiological scenario for two overlapping conditions.

However, studies assessing the relationship between food allergy and GORD show an overall association between 16 and 55% [26], thus far beyond what can be expected from pure coexistence of the two entities. In the mid-1990s, Iacono et al. described that 42% of infants with GORD symptoms and histologic oesophagitis clinically improved on a cow's milk-free diet and then worsened following antigen challenge [27]. Subsequently, Nielsen et al. showed that 56% of children with severe GORD were found to have CMA on double-bind or open challenge [28]. Recently, Yukselen et al. identified food allergy in 65 of 151 children with GORD refractory to medical therapy, of which 89% reacted to cow's milk, whilst a minority (11%) did so towards egg [29]. Notably, only half of those patients with GORD and food allergy had positive oral challenge and skin prick test and/or specific IgE; on the contrary, the other half could merely confirm the diagnosis by means of oral challenge.

In the past, some attempts had been made in order to elucidate the relationship between CMPA and GORD in the clinical setting by means of pH monitoring. However, these pH-only studies have led to conflicting results [25–32]. A particular phasic pH pattern characterized by a slow and progressive decrease in oesophageal pH between two feeds had been previously suggested as an effective tool for identifying patients with CMA-induced GORD by an Italian group [29, 30]. Nielsen et al. performed 48-h pH monitoring in 10 children with a severe GORD and CMA, with CM elimination diet at day 1 and CM challenge at day 2 [31]. Interestingly, they failed to find any difference in the reflux parameters between the two recording days. On the contrary, a Polish study confirmed the findings of the Italian groups showing that amongst the children with CMPA and GORD, pH-metric records showed a pattern of rapid increase of pH value after a meal with its subsequent gradual decrease [33].

However, only the introduction of combined impedance and pH monitoring could shed further light on this topic. Forty-eight-hour multichannel intraluminal impedance-pH monitoring in children with CMPA and suspected GORD has shown a significant increase in weakly acid reflux episodes during cow's milk challenge compared to elemental formula feeding [34]. Nevertheless, it was not possible to ascertain whether the decrease in reflux episodes was attributable to the enhanced gastric emptying because of the elemental formula or to the suppression of an underlining immune mechanism towards cow's milk antigens. This clinical finding, however, relies on the mechanisms addressed in a previous study showing how cow's milk induces severe gastric dysrhythmia and delayed gastric emptying in sensitized infants, thus triggering GORD and inducing reflex vomiting [18].

Albeit oesophageal manometry has no diagnostic yield in this clinical framework, a research study has found that both lower oesophageal sphincter (LOS) resting pressure and LOS length did not differ between children with primary GORD and CMPA-related GORD [35].

Conclusion

In conclusion, CMPA and GORD show an association between 16 and 55% in children. These data should induce paediatricians to screen for possible concomitant CMPA mainly in those infants and children with GORD unresponsive to medical treatment. Current ESPGHAN-NASPGHAN guidelines clearly advice a 2–4 week trial of protein hydrolysate or amino acid–based formula in infants with chronic regurgitation unresponsive to medical therapy, vomiting and failure to thrive [36].

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