

# Gastroesophageal reflux (GER) in children and adolescents with regard to food intolerance

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## Abstract

**Purpose:** The hypothesis put forward in the current study was that food intolerance can be a cause of gastroesophageal reflux (GER) affecting children with this pathology at various age. In order to confirm or exclude this hypothesis, the study objective was to determine the frequency of the cause-and-effect relationship between allergy to cow milk proteins and/or other food products and gastroesophageal reflux found in the study group of patients, and to establish diagnostic differentiation guidelines in GER caused by food intolerance, i.e. secondary vs primary GER.

**Material and methods:** A total of 735 children (428 boys – 58.2% and 307 girls – 41.8%; mean age  $\bar{x}$ =41.12 months  $\pm$ 25.03) with symptoms suggesting gastroesophageal reflux disease (GERD) were qualified for the study.

The diagnostic procedure included a 24 h pH-metry of the oesophagus, which was performed in all the study children. In 703 patients (411 boys – 55.9% and 292 girls – 39.7%) upper gastrointestinal endoscopy was carried out. Manometric examination of the oesophagus was performed in 232 children (123 boys – 16.7% and 109 girls – 14.8%). Allergological and immunological tests were done in 170 children with suspected allergy (91 boys – 12.4% and 79 girls – 10.7%). Contrast radiography of the upper gastrointestinal tract was performed in 78 children with respiratory symptoms (42 boys – 5.7% and 36 girls – 4.9%). Oral challenge test was used to differentiate primary GER from GER secondary to cow milk proteins intolerance or other food allergy in 138 children (72 boys – 9.8% and 66 girls – 8.9%).

**Results:** Based on the 24 h pH-metry of the oesophagus and endoscopic examination of the upper gastrointestinal tract, gastroesophageal reflux disease and/or reflux oesophagitis were

diagnosed in 138 study subjects (18.8%); mean age  $\bar{x}$ =23.36 months  $\pm$ 22.53. Positive oral food challenge test confirmed pathological GER secondary to cow milk protein allergy/other food hypersensitivity in 62 children (8.4%).

**Conclusion:** The current study revealed the existence of the cause-and-effect relationship between allergy to cow milk protein/other food products and GER in the study children at various age.

**Key words:** acid gastroesophageal reflux: primary, secondary; food allergy, oral food challenge test, children.

## Introduction

Gastroesophageal reflux (GER) occurs when stomach contents leak back involuntarily into the oesophagus due to functional insufficiency of certain elements of the antireflux barrier, particularly due to lower oesophageal sphincter (LES) dysfunction [1-4].

Pathogenetically, gastroesophageal reflux has been divided into primary and secondary [1,2,5-8]. Primary gastroesophageal reflux (idiopathic), depending on its intensity, can be physiological or pathological having typical or atypical manifestation.

Secondary gastroesophageal reflux is usually a pathological condition observed in such diseases as infections, allergies, as well as systemic, genetic, metabolic disorders and others [2,9,10].

Reflux of varied intensity may occur at any age, but in children it is intensified in the first months or years of life [2,4].

In approximately 40-50% of infants, GER is functional in nature, uncomplicated and regarded as physiological [11-13]. In this subgroup, in approximately 60-70% of children reflux symptoms subside spontaneously (usually between 10th-12th month of life); in 25%, the symptoms persist for over a year, while in the rest (ca. 5%) even longer (18th-24th month of life) [1,10-14].

In approximately 30% of children, shift of stomach contents into the oesophagus is so intensified that reflux becomes a pa-

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**Table 1.** Children treated in the Department of Children Diseases in Białystok, in the years 1992-1995 r., qualified for the study and subjected to clinical observation

Hospitalization and treatment of patients in the Department – study period (in years)	Children hospitalized due to various ailments	Children with suspected gastroesophageal reflux disease (GERD)		Children with suspected GERD and positive family history of alimentary disorders		Children with suspected GERD and negative family history of alimentary disorders	
		Number	Number [%]	Number	[%]	Number	[%]
1992/1993	2872	278	9.7	144	5.0	134	4.7
1994	2259	203	9.0	57	2.5	144	6.5
1995	2722	254	9.3	63	2.3	191	7.0
Total	7853	735	9.4	264	3.4	471	6.0

thology (primary or secondary) and usually causes troublesome symptoms from the oesophagus (typical), frequently enhanced by mucosal inflammation [1,10-15].

Reflux can also be responsible for diverse atypical complaints – respiratory, circulatory, neurological or for all-systemic manifestation [2,4,10]. Duration of reflux symptoms is changeable, as they may become chronic or recurrent.

The presence of clinical symptoms of GER can be associated with the co-occurrence of food allergy, especially cow milk protein intolerance (mainly in infancy) or other food products popular with children in the later period (secondary reflux) [6,9,10].

In the earliest developmental period, reflux may be caused by food allergy alone, at the later age, food intolerance may occur with GER [6-8,16-19].

Diagnostically and therapeutically, differentiation between primary (idiopathic) and secondary (related to food allergy) GER is essential.

The observations and clinical findings obtained in the last 10 years in the III Department of Children's Diseases in Białystok as well as the data reported by many researchers seem to confirm that there is a cause-and-effect relationship between gastrointestinal reflux and food allergy, mainly cow milk protein intolerance in infancy, and allergy to other food products at the older age [6-8,18,20,21].

**Research hypothesis** – food allergy can lead to acid gastroesophageal reflux in children at various age.

In order to confirm or exclude this hypothesis, the following study objective was formulated: 1) to determine the frequency of cause-and-effect relationship between allergy to cow milk proteins and/or other food products and acid gastroesophageal reflux found in the study group of patients; 2) to establish rules describing diagnostic differentiation guidelines in acid GER caused by food intolerance, i.e. secondary vs primary GER.

## Material and methods

### A. Patients' profiles

Within a 3-year period, i.e. in the years 1992-1995, 7853 children were hospitalized in the III Department of Children's Diseases, Medical University of Białystok (Tab. 1, Fig. 1).

Of them, 735 (9.4%) children were selected, with varied mono- and poly-organ symptoms suggesting gastroesophageal reflux disease (GERD).

According to age of the study children, the following symptoms caused by massive shift of the stomach contents back to the oesophagus were distinguished:

a) from the alimentary tract – intensive regurgitation, vomiting, irritability/sudden crying, ruminatio, food refusal/feeding disturbances, failure to thrive, abdominal pain, heartburn, belching/hiccups, bad breath (foetor ex ore), swallowing difficulty (dysphagia);

b) recurrent or chronic respiratory disorders – apnoea/desaturation, frequent pharyngitis/tonsillitis, bronchitis, obturative/spastic bronchitis, pneumonia, persistent cough, wheezing;

c) neurological symptoms suggesting GERD – back arching, flaccidity, pallor, disorders of consciousness, stiff neck (torticollis);

d) and others – e.g. anaemia.

### B. Diagnostic investigations

General characteristics of diagnostic investigations performed in 735 (100.0%) children suspected of GER has been presented in Tab. 2.

The study group consisted of 428 boys (58.2%) and 307 girls (41.8%), aged 1.5-168 months; mean age  $x=41.12$  months (3 and 5/12 years)  $\pm 25.03$ .

Diagnostic procedures included 24 h pH-metric testing of the oesophagus done in all the 735 study children. The following pH monitoring parameters were analysed: the number of episodes of acid GER (a decrease of intraesophageal pH below 4.0), the number of episodes of acid GER lasting more than 5 minutes (so-called "long episodes"), reflux index (total and supine – in both leads) that measures the percentage of time that the pH is below 4.0 within 24-hour intraesophageal pH monitoring [6,7,14,17,22-29]. Endoscopic examination of the upper gastrointestinal tract performed in 703 patients (411 boys – 58.5% and 292 girls – 41.5%, aged 4 – 168 months; mean age  $x=43.20$  months (3 and 7/12)  $\pm 26.74$ ) [8,15,26,27,29,30].

A total of 232 (31.5%) children (123 boys – 16.7% and 109 girls – 14.8%, aged 4-102 months; mean age  $x=25.42$  months  $\pm 21.47$ ) with suspected GER underwent oesophageal manometric investigations at the time of final diagnosis to assess motoric function of the oesophagus, especially of its lower sphincter (LES) [26,27,31]. Allergological and immunological tests were performed in 170 (23.1%) children (91 boys – 12.4% and 79 girls – 10.7%), mean age  $x=23.47$  months  $\pm 19.23$  to search for allergic cause of GER [19,32].

Figure 1. Qualification of hospitalized children with symptoms suggesting gastroesophageal reflux disease (GERD). Diagnostic examinations confirming or excluding gastroesophageal reflux (GER)

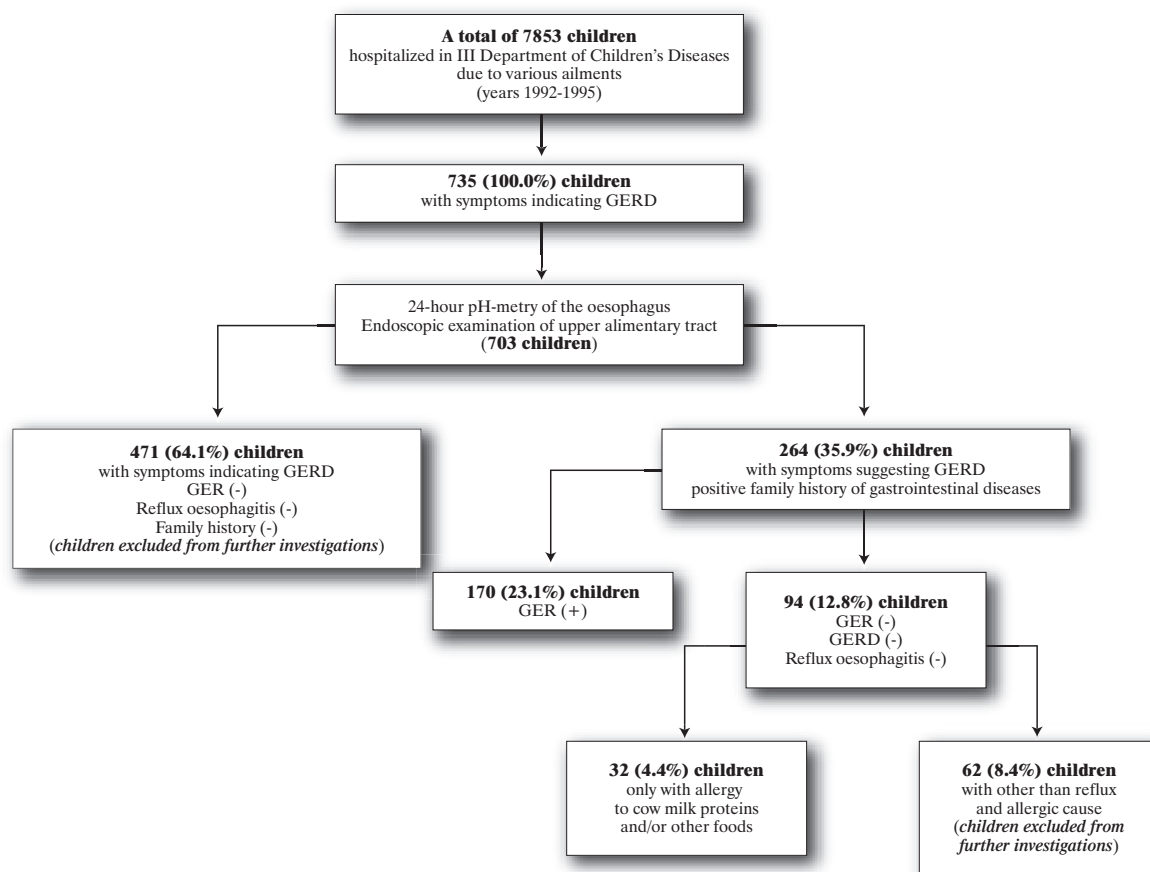


Table 2. Diagnostic investigations in 735 children with suspected gastroesophageal reflux disease (GERD)

Preliminary diagnostic investigation	Study children			Age of study children from – to Mean age [x]
	Gender	N	%	
24-hour oesophageal pH-metry	boys	428	58.2	> 1.5-168 months (41.12 +/- 25.03)
	girls	307	41.8	
	total	735	100.0	
Endoscopic examination of oesophagus, stomach and duodenum	boys	411	55.9	>4-168 months (43.20 +/- 26.74)
	girls	292	39.7	
	total	703	95.6	
Oesophageal manometry	boys	91	12.4	>4-102 months (23.47 +/- 19.23)
	girls	79	10.7	
	total	170	23.1	
Allergological and immunological investigations	boys	123	16.7	>4-102 months (25.42 +/- 21.47)
	girls	109	14.8	
	total	232	31.5	
Radiological examination of upper alimentary tract with barium contrast	boys	42	5.7	>4-102 months (23.36 +/- 22.53)
	girls	36	4.9	
	total	78	10.6	

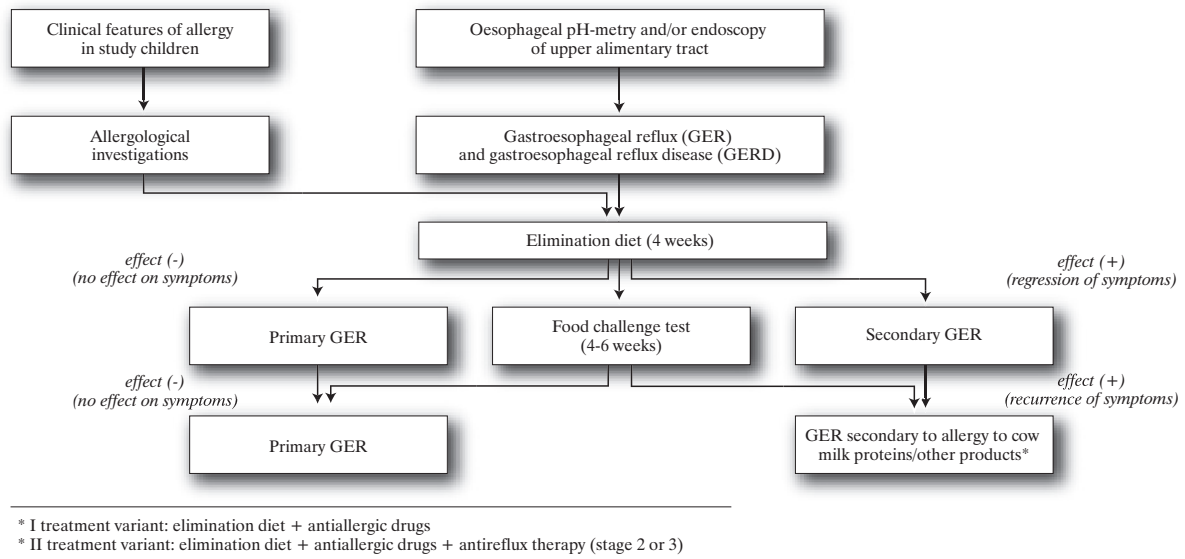
The upper gastrointestinal contrast X-ray examination was done in 78 (10.6%) children with respiratory symptoms (42 boys – 5.7% and 36 girls – 4.9%; mean age  $x=23.26$  months  $\pm 22.53$ , to look for evidence of the causative role of GER in their development, and to search for likely developmental anomalies frequently associated with defects of the trachea, the bronchi or the diaphragm [27,28,33,34].

Searching for a cause of GER other than food allergy, the respective findings of accessory investigations were analysed.

Chest X-ray pictures and computer tomography of nasal sinuses were used to evaluate the type, location and character of the associated pathology.

In order to confirm or exclude the infectious cause of GER, the following parameters were estimated: erythrocyte sedimen-

**Figure 2. Algorithm of management differentiating between primary and secondary GER in 138 study children with suspected allergy to cow milk proteins and/or other foods based on elimination diet and challenge test outcomes**



tation rate (ESR), C-reactive protein (CRP), antistreptolysin reaction (ASR), blood smear morphology, proteinogram, protein immunoelectrophoresis, immunoglobulins A, M, G, and iron concentration.

Bacteriological analysis involved testing of blood, urine, faeces, bile, as well as pharyngeal and nasal swabbings in some children.

Metabolic screening of blood (e.g. lactate acid, ammonium, acid-base equilibrium parameters) was performed to exclude the metabolic cause of the disease, while pilocarpin test (sweat chloride) was used to exclude mucoviscidosis in these children [2,4,9,10].

We used our own algorithm of diagnostic and therapeutic management to differentiate primary (idiopathic) from secondary GER (Fig. 2) in 138 children with gastroesophageal reflux disease (GERD) out of 170 with acid GER [8].

As food allergy was believed to trigger or enhance GER in the study group of children, oral challenge test was conducted to determine its allergic background [6,7,18,20,32].

At the first stage, elimination diet was introduced for 4 weeks to exclude food products suspected of allergisation, including cow milk or others (depending on the child's age).

Instead, the youngest patients received milk substitutes – casein hydrolysates, whey proteins or a mixture of free amino acids. Older children had hypoallergic diet without harmful products [10,16,32].

The patients who showed clinical improvement (regression or alleviation of symptoms) were subjected to oral food challenge with a milk mixture, dairy products or other harmful foods which they had consumed before (open method) [32].

The diagnosis of allergy to cow milk protein and/or other foods was made when the symptoms subsided during the application of elimination diet and the food challenge was positive (the symptoms recurred).

Intensity of reflux symptoms, especially those typical (from

the alimentary tract), was assessed using a “stipulated” score system (1-5):

- mild short-term symptoms (up to 2 weeks), occurring episodically or recurring periodically – 1,
- chronic symptoms (over 2 weeks), mild in intensity – 2,
- chronic symptoms of considerable intensity – 3,
- chronic symptoms of considerable intensity, with a periodical tendency to exacerbate – 4,
- chronic symptoms of high severity – 5.

In order to obtain clinical evidence of the allergic factor in GER, especially in older children (over 3 years of age), constitutional features of allergy according to Marks were considered [35].

Once the diagnosis had been made, proper therapy was instituted and clinical observation was recommended at 6-week intervals (prospective studies).

Each patient was subjected to physical examination at every check-up. General condition and competence of systems and organs, especially those at risk of GER effects, were assessed.

## Results

As shown in Tab. 3, of 735 preliminary patients, 264 (35.9%) children of both genders with suspected gastroesophageal reflux disease and family history of gastrointestinal disorders were qualified for the study.

The 24 h pH-metric testing of the oesophagus, endoscopic examination of the upper gastrointestinal tract and histopathological investigation of oesophageal mucosa specimens confirmed acid gastroesophageal reflux in 170 (23.1%) patients. GERD was diagnosed in 138 of them (18.8%), including 54 (7.3%) with reflux oesophagitis. In the remaining 565 (76.9%) children, including 94 (12.8%) with family history of gastroin-

**Table 3.** Examination results in 735 children with suspected gastroesophageal reflux disease (GERD), hospitalized in the Department of Children Diseases in Białystok, in the years 1992-1995

Diagnostic investigation	Study children		Acid gastroesophageal reflux											
			present										absent	
			pathological						physiological					
			total		oesophageal reflux disease		reflux inflammation of oesophageal mucosa							
N	%	N	%	N	%	N	%	N	%	N	%			
											565	76.9		
24-hour oesophageal pH-metry	735	100.0			84	11.4	-	-			94*	471	12.8*	64.1
			138*	18.8*					32*	4.3*				
Endoscopic examination of oesophagus, stomach and duodenum	703	95.6			-	-	54	7.3			649**		88.3**	

\* A total of 264 (35.9%) children with suspected oesophageal reflux disease and positive family history of gastrointestinal disorders;

\*\* In these patients, inflammation of oesophageal mucosa was not macroscopically or histopathologically confirmed

testinal disorders, neither pathological GER nor inflammatory changes in the oesophageal mucosa were found.

Positive oral food challenge test confirmed secondary pathological GER in 62 children (8.4%), mean age  $x=21.53$  months  $\pm 17.79$ .

In the remaining 76 (10.3%) children, mean age  $x=25.20$  months  $\pm 27.28$ , primary GER was diagnosed.

## Discussion

Recent years have brought an increase in the number of clinical observations indicating that gastroesophageal reflux (GER) may have an allergic background.

In children, especially in the youngest (infancy), cow milk allergy (cma) is the most common cause of GER [6,7,9,10,18-20].

In older children, GER can be a clinical manifestation of body hypersensitivity to dairy meals, other food products and inhaled air allergens [36-38].

The causal relationship between these two pathological conditions, i.e. GER and cow milk allergy is indicated by age (most frequently infancy) and similarity of clinical symptoms typical of both pathologies [1,6].

Forget et al. have suggested that these two disorders are most frequent in the first months of life and tend to disappear after the first year of life. According to these authors, their incidence is similar, ranging from 1% to 10% [39].

Hill et al., studying the diversity of symptoms in the course of hypersensitivity to cow milk proteins, revealed that 6% of the youngest patients had gastroesophageal reflux symptoms [40].

However, other authors have reported that the percentage of secondary GER in the youngest children with cow milk allergy is substantially higher and reaches 16-40% [6,7,18].

In a group of vomiting infants, Staiano et al. found pathological acid GER to coexist with cow milk allergy in 16% of the children and cow milk allergy alone in the same percentage of patients [18].

Cavataio et al. in prospective studies observed a co-occur-

rence of cow milk allergy in 41.7% infants with acid GER [6,7]. The authors, comparing the symptoms of secondary and primary GER found no differences in age, gender or clinical picture between these groups of patients.

Kaczmarek et al. were the first in Poland to make similar clinical observations indicating the causal role of food allergy in triggering acid GER [3,8,9,16].

In the current study, the share of allergy to cow milk proteins and/or other food products in secondary GER accounted for 36.5%, while in GERD for 44.9% of children at various age.

We instituted our own algorithm of diagnostic and therapeutic management in order to properly differentiate primary (idiopathic) from secondary GER. As food allergy was considered to be a potential cause of GER, temporary elimination of harmful food products was introduced for the period of 4-6 weeks.

Then, the allergic patients who responded well to elimination diet (regression of secondary GER symptoms), were subjected to challenge test with cow milk and/or other food product to supply evidence for the cause-and-effect relationship. Depending on the patient's age and type of clinical symptoms, the challenge test was either open or blind, placebo-controlled. [16,32].

The recurrence of symptoms during challenge test confirmed the diagnosis of food allergy and its share in secondary GER.

In addition to elimination diet and challenge test, complete differential diagnosis of GER is essential and includes allergological and immunological investigations, radiological examinations of the chest, upper gastrointestinal tract, lateral sinuses of the nose, as well as biochemical, metabolic, bacteriological studies and others [2,4,9,10].

In the children with a causal role of food hypersensitivity in triggering GER, elimination diet was found to have high nutritional and therapeutic values both in the treatment of allergy and GER, and in some of the patients no antireflux drugs had to be administered.

However, when complete improvement is not achieved, antiallergic and eventually antireflux drugs should be administered [6-8,10].

Those children who did not present with a recurrence of symptoms during food challenge had primary type of GER and underwent a classic variant of antireflux treatment (prokinetic drugs and/or regulating gastric acid secretion) [2,8,10,15,17,41,42].

## Conclusion

The current study revealed the existence of the cause-and-effect relationship between allergy to cow milk protein/other food products and GER in the study children at various age.

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