

Gastroesophageal reflux in children and adolescents. Clinical aspects with special respect to food hypersensitivity

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Abstract

Purpose: Gastroesophageal reflux (acid GER), primary and secondary, has a wide spectrum of clinical symptoms and occurs at developmental age.

The study objective was to elaborate the clinical profile of symptoms and to determine whether there are any differences in clinical manifestations between the two acid GER conditions, i.e. primary and secondary to cow milk allergy and/or other food allergy (CMA/FA).

Material and methods: The study involved 264 children of both genders and at various age, with diverse reflux symptoms from one or many organs and with a positive family history of alimentary tract diseases. Based on preliminary diagnostic tests, the children were divided into groups. In 138 children, pathological acid GER, primary and secondary to CMA/FA, was recognized.

Results: The profile of clinical symptoms observed in 264 children with suspected gastroesophageal reflux disease (GERD) was elaborated according to their frequency. Among differentiating symptoms the most common were: vomiting (12.1%), bronchitis (10.9%) and pneumonia (9.6%). In the group of 138 GER children, 32 (23.2%) had monosystemic symptoms, in the other 106 patients (76.8%) many systems were affected. The most frequent reflux symptoms were: in primary GER (group 2) – alimentary tract disorders (28.6%), pneumonia and bronchitis (20.7%) and neurological symptoms with torticollis (7.4%); in secondary GER (group 3) – alimentary tract disorders: vomiting and anxiety/crying (25.2%); pneumonia and bronchitis (19.4%). In 23 children (37%) with secondary GER, typical allergic symptoms were found to coexist. The 138 GER

patients underwent allergologic and immunologic tests to confirm the allergic background of symptoms.

Conclusion: Clinical symptoms caused by the presence of secondary acid GER are non-specific, being identical or similar to those observed in primary acid GER. Allergologic and immunologic tests are useful to confirm or exclude the relationship between GER and CMA/FA in the study children.

Key words: acid gastroesophageal reflux: primary, secondary; food allergy; clinical manifestation; allergologic and immunologic tests; children.

Introduction

According to the generally accepted definition, gastroesophageal reflux (acid GER) is the involuntary, temporary or permanent passage of gastric contents into the esophagus as the result of defective functional competence of the respective elements of the antireflux barrier, mainly of the lower esophageal sphincter (LES) with its abnormal resting tension and disturbed motor activity of the upper alimentary tract [1-7].

Pathogenetically, reflux can be divided into primary GER (physiologic or pathologic), secondary GER and gastroesophageal reflux disease (GERD) [8-12].

Gastroesophageal reflux disease (GERD) is a clinical condition manifested by differentiating symptoms due to diagnostically confirmed pathological GER (primary or secondary).

Reflux esophagitis (RE) is the most common local complication of GERD [2,13-16].

Numerous in-depth clinical observations conducted by various authors on the population of developmental age and adults have confirmed that GER is responsible for complex and abundant clinical symptomatology, with different organs and systems involved (alimentary tract, respiratory system, circulatory system, central nervous system, all-systemic ailments) in isolated or associated form.

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Table 1. A list of reflux symptoms [17]

Typical	Reflux symptoms
	Atypical
- regurgitation	- hoarseness
- vomiting	- laryngitis (stridor)
- hematemesis and/or melaena	- obturative bronchitis (wheezing)
- body weight and/or height deficiency	- spastic bronchitis
- abdominal pain	- pneumonia
- retrosternal pain	- persistent cough
- food refusal	- asthmatic syndrome
- heartburn	- anemia
- hiccups/belching	- changes in muscle tension of the nape and/or trunk (arching, myotonia)
- irritability, anxiety/paroxysmal crying	- Sandifer's syndrome
- dysphagia	- ALTE syndrome (apnea, cyanosis, pallor, consciousness disturbances, bradycardia)
- odynophagia	

Table 2. Overall presentation of types and frequency of clinical symptoms of esophageal reflux disease with respect to age (according to Salvatore et al.) [23]

Reflux symptoms	Infants	Children	Adults
Vomiting	++	++	+
Regurgitation	++++	+	+
Heartburn	?	++	+++
Abdominal pain	?	+	++
Retrosternal pain	?	+	++
Dysphagia	?	+	++
Paroxysmal irritability/crying	+++	+	-
Anemia	+	+	+
Body weight deficiency	++	+	-
Abnormal posturing (Sandifer's s.)	++	+	-
Hiccups	++	+	+
Dental erosion (caries)	?	+	+
Hoarseness/aphonia	?	+	+
Chronic cough/bronchiopulmonary symptoms	+	++	+
Wheezing/laryngitis/ear problems	+	++	+
Laryngomalacia/stridor	+	++	-
Asthmatic syndrome/sinusitis	-	++	+
Laryngostenosis	-	+	+
ALTE (SIDS/apnea)	+	-	-
Bradycardia	+	?	?
Sleep disturbances	+	+	+
Impaired quality of life	++	++	++
Esophagitis	+	+	++
Esophageal stenosis or shortening	-	(+)	+
Barrett's esophagus/adenocarcinoma	-	(+)	+

++++ - predominant; +++ - very common; ++ - common; + - possible; (+) - rare; - - absent; ? - unknown

Most symptoms fall into two categories: typical and atypical ones [3,17-22]. The spectrum of acid GER symptoms has been presented in *Tab. 1* [17].

Salvatore et al. carried out a more up-to-date clinical analysis of reflux symptoms (2004) according to patients' age (*Tab. 2*), showing a considerable similarity in their type and differentiation in frequency in comparison to earlier overall analyses of this type [23].

In approximately 30% of children, enhanced passage of gastric contents into the esophagus becomes a pathology (primary or secondary) and usually causes troublesome symptoms, mainly from the esophagus (typical) [1,11,13,21,22].

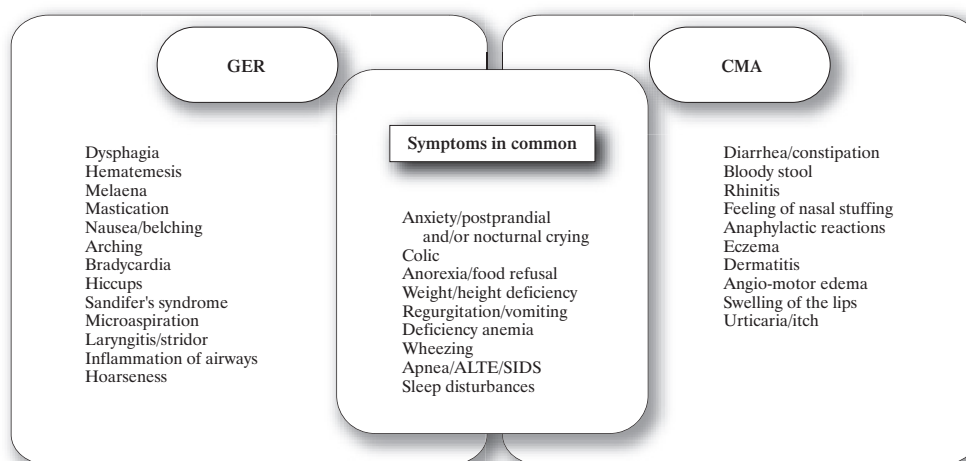
GER can also be responsible for a number of differentiated atypical symptoms, with respiratory, circulatory, neurological or all-systemic manifestations [2,7,13].

Duration of reflux symptoms varies, as they are usually chronic or recurrent.

Secondary GER is a pathologic phenomenon that usually occurs in the course of already existing disorders, such as infectious, allergic, neurologic, systemic, genetic, metabolic and others [2,11,13].

Clinical symptoms of GER may have a causal association or may coexist with food hypersensitivity, especially with allergy to cow milk proteins (mainly in infancy) and/or other food prod-

Figure 1. Profile of clinical symptoms in the course of GER and CMA [13]



ucts commonly consumed by older children (secondary reflux) [10,11,13].

Potential ethiopathogenic relationships between GER and CMA, the most common early childhood ailments, have been investigated for a few years now [8-10,24].

Not only the age of patients, but also the whole range of clinical symptoms these two entities have in common (e.g. regurgitation/vomiting, colic, anxiety, insufficient weight increase and others) (Fig. 1), seem to justify an attempt to prove the existence of mutual relations [13].

In older children, GER which is clinical manifestation of food hypersensitivity presents with such differentiated symptoms as vomiting/regurgitation, ruminatio, belching/hiccups, abdominal pain, wheezing, paroxysmal cough, bronchitis, hoarseness and others [2,6,7,23].

However, literature evidence for the association between GER and food hypersensitivity in older children is scarce [9-12,24-26].

The study objective was to: elaborate a clinical profile of symptoms (similarities and differences) in children with secondary acid GER, having a causal association with food hypersensitivity, and with primary acid GER.

Material and methods

A total of 735 children with suspected GERD, hospitalized in III Department of Pediatrics, Medical University of Białystok in the years 1992-1995, underwent diagnostic examinations (24-hour intraesophageal pH-metry and endoscopic examination of the upper alimentary tract). Among them, the major group consisted of 264 (35.9%) children of both genders, with differentiated mono- and polysystemic symptoms and with a positive family history of alimentary disorders.

Allergologic and immunologic tests were performed in children with diagnosed pathologic acid GER to confirm its allergic cause (secondary GER) and to differentiate it from primary GER (idiopathic).

a) Skin "prick tests" – done with:

- a set of native food allergens (fresh);
- a set of inhalatory commercial allergens (Smith Kline Beecham – USA).

These tests were performed once in 71 children with pathologic GER and in 32 patients with only CMA/FA at various age in order to confirm or exclude early IgE-dependent hypersensitivity to food and/or inhalatory allergens (atopic factor).

b) Total serum (tIgE)

Total serum IgE was determined using Fluoro-FAST method (3M Diagnostic Systems, USA) in 170 children and this determination was significantly helpful in differentiation of pathogenetic IgE-dependent and independent mechanisms involved in food allergy. The tIgE level in serum was considered elevated when its value was >50 IU/ml.

As a single measurement of total IgE has a limited specificity in atopy recognition, other specific immunoglobulins of this class have been determined for chosen food allergens.

c) Qualitative and quantitative assessment of specific IgE against food allergens (a-s IgE) and inhalatory allergens (i-s IgE), with Fluoro-FAST method (3M Diagnostic Systems, USA).

Determination of allergen-specific immunoglobulins in the study children not only confirmed IgE-dependent pathomechanism of food allergy, but they also allowed recognition of sensitizing food allergens. It was also helpful whenever, for various reasons, prick tests could not be performed or their results were doubtful.

We performed qualitative and quantitative assessment of a-s IgE/and i-s IgE in 103 patients with suspected allergy, including those with positive prick tests, with food and/or inhalatory allergens and elevated serum IgE.

Specific IgE were those in class 2-5 and included:

- a-s IgE against cow milk proteins, hen egg white, soya protein, fish protein, oranges;
- i-s IgE against grass pollen, tree pollen, bush and weed pollen, house dust mites and cat fur, determined in serum.

d) Eosinophilia

Eosinophilia was assessed once in peripheral blood smear

Table 3. Study results in 735 children with suspected gastroesophageal reflux disease (GERD), hospitalized in III Department of Pediatrics in the years 1992-1995

Diagnostic investigation	Study children		Gastroesophageal reflux													
			Present													
			Pathologic						Physiologic		Absent					
			Total		Esophageal reflux disease		Reflux mucosal esophagitis									
N	%	N	%	N	%	N	%	N	%	N	%					
24-hour intraesophageal pH-metry	735	100.0			84	11.4	-	-					565	76.9		
Endoscopy of esophagus, stomach and duodenum	703	95.6	138*	18.8*	-	-	54	7.3	32*	43*			94*	471	12.8*	64.1
													649**		88.3**	

*A total of 264 (35.8 %) children with GERD and positive family history of alimentary disorders.

** Mucosal esophagitis was not confirmed macroscopically or histopathologically in these patients.

Table 4. Classification of 264 children with suspected gastroesophageal reflux disease into study groups (at the time of diagnosis)

Study groups	Gender	Study children with reflux symptoms							
		Number		Age range in months					
				>1.5 m – 4 m		>4 m – 16 m		>16 m – 102 m	
		N	%	N	%	N	%	N	%
Group 1 N=32 Physiologic GER	Boys	17	6.4	17	6.4	-	-	-	-
	Girls	15	5.7	15	5.7	-	-	-	-
Group 2 N=76 Primary GER	Boys	39	14.8	-	-	23	8.7	16	6.0
	Girls	37	14.0	-	-	21	7.9	16	6.0
Group 3 N=62 GER + CMA/FA	Boys	33	12.5	-	-	16	6.1	17	6.4
	Girls	29	11.0	-	-	14	5.3	15	5.7
Group 4- reference N=32 CMA/FA	Boys	19	7.2	-	-	7	2.6	12	4.5
	Girls	13	4.9	-	-	5	1.9	8	3.0
Group 5 N=62 GER (-) + CMA/FA (-)	Boys	32	12.1	-	-	8	3.0	24	9.1
	Girls	30	11.4	-	-	10	3.8	20	7.6
Total		264	100.0	32	12.1	104	39.4	128	48.5

in 138 children with pathologic GER and in 32 patients with CMA/FA alone.

It was a useful laboratory indicator confirming the allergic cause of symptoms from the alimentary tract and other organs.

The percentage value of eosinophilia was treated as abnormal when >5%.

Classification of patients into study groups

Based on preliminary diagnostic tests carried out in 264 children, as well as using dietary analysis and the findings obtained from elimination diet test and oral food challenge in 138 of them, the children were classified into study groups (Tab. 3, 4; Fig. 2).

Of 170 (64.4%) patients with diagnosed acid GER (89 boys, 81 girls), 32 (12.1%) of the youngest infants with physiologic GER (group 1; mean age $x=2.2$ months ± 0.48) were excluded from further analysis and clinical observation.

The remaining 138 (52.3%) children had primary and secondary pathologic GER, and were classified into groups 2 and 3.

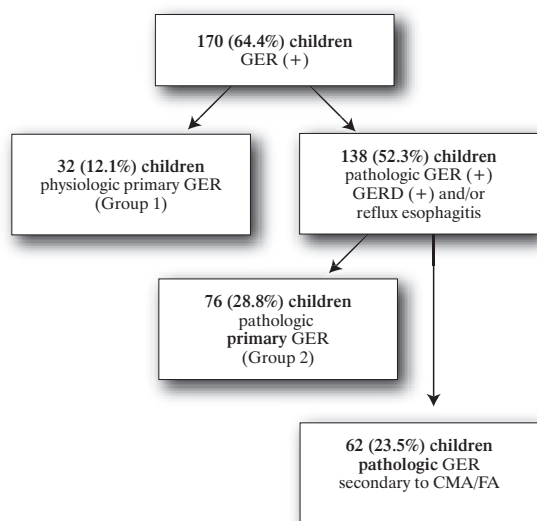
Group 2 included 76 (28.8%) patients (39 boys – 14.8%; 37 girls – 14.0%), aged 4-102 months (mean age $x=25.20$ m ± 27.28), with pathologic primary GER.

Group 3 contained 62 (23.5%) patients (33 boys – 12.5%; 29 girls – 11.0%), aged 4-74 months (mean age $x=21.53$ m ± 17.79), with secondary pathological GER. Ninety-four (35.6%) of 264 patients with symptoms suggesting GERD, positive family history of alimentary disorders and with non-confirmed pathologic GER were classified into:

– group 4 – 32 (12.1%) patients (19 boys – 7.2%; 13 girls – 4.9%) aged 7 months – 69 months (mean age $x=23.70$ m ± 12.63) with pathologic symptoms against a background of diagnosed allergy to cow milk proteins and/or other food products (the so called reference group);

– group 5 – 62 (23.5%) patients (mean age $x=31.3$ months

Figure 2. Further classification of 170 children with diagnosed acid GER into study groups. Prospective clinical observation with the use of differentiating diagnostic-therapeutic algorithm



±27.98), with non-confirmed reflux or allergic cause of the existing symptoms. These children were excluded from further analysis and clinical observation.

Patients classified into the above groups did not differ significantly (p=ns) with respect to age and gender.

Results

Clinical profile of the study children

Twenty-four clinical reflux symptoms observed in 264 children with GERD and a positive family history of alimentary disorders according to their frequency have been presented in Tab. 5. Among them the most common were: vomiting (12.1%), bronchitis (10.9%) and pneumonia (9.6%), the least common being anemia (1.3%), apnea (1.0%) halitosis (1.0%), nasal obstruction (coryza) (0.6%), and dysphagia (0.4%).

The frequency of pathologic acid GER-dependent symptoms, isolated or associated from the alimentary tract, respiratory system and nervous system in 138 children, has been presented in Tab. 6.

Table 5. Type and frequency of clinical symptoms in the study children (suspected esophageal reflux disease, positive family history of alimentary ailments)

No	Clinical symptoms Type	Incidence	
		N=478	%
1.	Vomiting	58	12.1
2.	Bronchitis	52	10.9
3.	Pneumonia	46	9.6
4.	Abdominal pain	39	8.2
5.	Regurgitation	32	6.7
6.	Food refusal	32	6.7
7.	Ruminatio	31	6.5
8.	Anxiety/crying	23	4.8
9.	Neurological symptoms*	21	4.4
10.	Obturative bronchitis	21	4.4
11.	Weight deficiency	19	4.0
12.	Chronic cough	15	3.1
13.	Belching / hiccups	12	2.5
14.	Coexistence of vesicoureteral reflux	12	2.5
15.	Heartburn	11	2.3
16.	Pharyngitis / laryngitis	9	1.9
17.	Spastic bronchitis	7	1.5
18.	Wheezing / dyspnea and/or paroxysmal cough	8	1.7
19.	Torticollis**	8	1.7
20.	Anemia	6	1.3
21.	Apnea	5	1.0
22.	Halitosis (foetor ex ore)	5	1.0
23.	Nasal obstruction (coryza)	3	0.6
24.	Dysphagia	2	0.4

* – arching, myotonia, cyanosis, pallor, disturbances of consciousness; ** – coexistence with neurological symptoms

Isolated symptoms (typical) from the alimentary tract were found in 24 (17.4%) children, from the respiratory system (atypical) in 8 (5.8%). In total, 32 (23.2%) of 138 young patients had monosystemic GER symptoms. The remaining 106 (76.8%) showed polysystemic symptoms (associated) from the alimentary, the respiratory and the central nervous system (92; 66.7%), the alimentary and the nervous system (9; 6.5%), and the respiratory and the nervous system (5; 3.6%).

Table 6. Frequency of isolated and associated ailments from various organs/systems in 138 children with pathologic acid GER: primary (group 2) and secondary to cow milk proteins and/or other foods (group 3)

Monosystemic disorders			Polysystemic disorders		
Type of disorder	N	%	Type of disorder	N	%
Alimentary system*	24	17.4	alimentary system + respiratory system***	81	58.7
			alimentary system + respiratory system + nervous system****	11	8.0
Respiratory system**	8	5.8	alimentary system + nervous system*****	9	6.5
			respiratory system + nervous system	5	3.6
Total	32	23.2	138 – 100.0 %	106	76.8

*r with vesicoureteral reflux – 1 (0.7 %) child; ***r with vesicoureteral reflux - 8 (5.8 %) children; ****a with asthma – 9 (6.5 %) children; *n with anemia – 3 (2.2 %) children; **n with anemia – 3 (2.2 %) children; ***** with Sandifer’s syndrome – 4 (2.9 %) children; ***** with Sandifer’s syndrome – 4 (2.9 %) children; *b with Barrett’s esophagus – 1 (1.3 %) children

Table 7. Comparative analysis of type and frequency of clinical symptoms in study groups of children with pathologic acid GER: primary (group 2) and secondary to CMA/FA (group 3)

Primary gastroesophageal reflux (2)			Secondary gastroesophageal reflux (3)		
Type	Frequency		Type	Frequency	
	N=188	%		N=139	%
Pneumonia	20	10.6	Vomiting	20	14.4
Bronchitis	19	10.1	Bronchitis	16	11.5
Regurgitation	15	8.0	Anxiety/crying	15	10.8
Vomiting	14	7.4	Neurological symptoms	13	9.3
Masticatio (Ruminatio)	14	7.4	Pneumonia	11	7.9
Food refusal	11	5.8	Food refusal	10	7.2
Obturator bronchitis	10	5.3	Abdominal pain	9	6.5
Weight deficiency*	10	5.3	Wheezing/dyspnea and/or paroxysmal cough	8	5.8
Coexistence of vesicoureteral reflux	9	4.8	Weight deficiency	6	4.3
Abdominal pain	8	4.2	Regurgitation	5	3.6
Belching/hiccups	8	4.2	Masticatio (Ruminatio)	5	3.6
Heartburn	8	4.2	Chronic cough	5	3.6
Anxiety/crying	8	4.2	Obturator bronchitis	4	2.9
Chronic cough	8	4.2	Heartburn	3	2.2
Neurological symptoms	8	4.2	Anemia	3	2.2
Torticollis	6	3.2	Halitosis (foetor ex ore)	2	1.4
Halitosis (foetor ex ore)	3	1.6	Torticollis	2	1.4
Spastic bronchitis	3	1.6	Spastic bronchitis	1	0.7
Anemia	3	1.6	Belching/hiccups	1	0.7
Dysphagia	2	1.1	-	-	-
Apnea	1	0.5	-	-	-
Coexisting allergic symptoms N=23			Generalized dermatitis	9	39.1
			Urticaria	4	17.4
			Rhinitis	4	17.4
			Itch	3	13.0
			Chronic diarrhea	3	13.0

*Barrett's esophagus – in 1 child

Tab. 7 presents a comparative analysis of the type and frequency of clinical symptoms found at the time of diagnosis in the study groups of 138 children with pathological acid GER: primary (group 2) and secondary to CMA/FA (group 3).

The most common reflux symptoms included:

- in primary GER (group 2) – alimentary manifestations in the following order: vomiting, ruminatio, food refusal (28.6% in total); pneumonia and bronchitis (20.7% altogether), and neurologic symptoms with torticollis (7.4%);

- in secondary GER (group 3) – alimentary manifestations: vomiting and anxiety/crying (25.2% in total); bronchitis and pneumonia (19.4% in total).

Less common were:

- in group 2 – obturator bronchitis and body weight deficiency (with the same frequency 5.3%), as well as other symptoms, including abdominal pain, belching/hiccups, heartburn and anxiety/crying (16.8% altogether), and chronic cough (4.2%);

- in group 3 – typical symptoms, such as anorexia, abdominal pain and weight deficiency, regurgitation and rumination (with the same frequency; 25.2% altogether); wheezing with

dyspnea and/or paroxysmal cough, chronic cough and obturator bronchitis (12.3% altogether).

The least frequent symptoms included:

- in group 2 – halitosis (foetor ex ore), spastic bronchitis and anemia (with the same frequency 1.6%); moreover, dysphagia (1.1%), exceptionally apnea attacks (0.5%);

- in group 3 – with the same frequency: heartburn and anemia (2.2% each), halitosis (foetor ex ore) and torticollis (1.4% each), very seldom spastic bronchitis and belching/hiccups (0.7%).

Nine children (11.8%) with primary GER (group 2) were additionally diagnosed with vesicoureteral reflux.

Interesting is that in 23 (37.0%) children with secondary GER (group 3) non-reflux allergic symptoms were found to coexist.

All the ailments were almost similar and their frequency did not differ much between both groups.

Results of allergic and immunologic tests

in 138 study children with pathologic acid GER

Results of allergic and immunologic tests performed in 138 study children with pathologic acid GER at the time of diagnosis

Table 8. Results of allergologic and immunologic tests in 138 children with pathologic acid GER (at the time of establishing diagnosis)

Type of examination	Study children				
	Primary GER (group 2, n=76)		GER secondary to CMA/FA (group 3, n=62)		
	N	%	N	%	
Positive family history of allergy	9	11.8	43	69.4	
Atopy in family	3	3.9	25	40.3	
Positive skin-prick tests with allergens	native food allergens	0	0.0	28	45.2
	commercial inhalatory allergens	4	5.3	8	12.9
	food and inhalatory allergens	0	0.0	20	32.3
tIgE levels	>50-100 IU/ml	3	3.9	18	29.0
	>00 IU/ml	0	0.0	16	25.8
sIgE (class 2-5) against:	food allergens	0	0.0	17	27.4
	inhalatory allergens	0	0.0	4	6.5
	food and inhalatory allergens	0	0.0	8	12.9
Eosinophilia of peripheral blood	>5 – 8%	5	6.5	24	38.8
	>8 – 15%	0	0.0	18	29.0
Constitutional features (clinical hallmarks) of allergy – (min.2)	5	6.6	19	30.6	

were analyzed in order to confirm the allergic cause of clinical symptoms (Tab. 8).

In group 3 consisting of 62 children with GER secondary to CMA/FA, most patients (43; 69.4%) had a positive allergic family history (allergy found among the closest relatives). This feature was the least common in group 2, i.e. in only 9 patients out of 76 with pathologic primary GER (11.8%).

Diverse allergic – non-reflux symptoms coexisted in 23 (37.1%) of 62 children in group 3, but were absent in group 2 patients.

Constitutional features of allergy were observed most often in group 3 – 19 patients (30.6%) as compared to 5 (6.6%) from group 2. In group 2, three children had elevated level of total IgE (tIgE) and in two eosinophilia was increased.

Positive results of skin-prick tests: with food allergens were obtained in 28 children (45.2%) in group 3.

Positive results of tests with food and inhalatory allergens referred to 20 patients (32.3%) in group 3.

Positive results of tests with only inhalatory allergens were found in 8 children (12.9%) from group 3 and in 4 (5.3%) from group 2, all with a positive family history.

Total serum IgE level in peripheral blood was elevated (>50-100 IU/ml) in 18 patients (29.0%) from group 3. Only 3 children (3.9%) from group 2, with a positive family history of allergy, showed increased tIgE level (values in the range above).

The values of tIgE >100 IU/ml were found in 16 patients (25.8%) from group 3.

The presence of specific IgE (sIgE) in the serum was detected in 29 children (46.8%) from group 3. They were positive (class 2-5) against food allergens – in 17 (27.4%); against food and inhalatory allergens – in 8 (12.9%) and against inhalatory allergens alone – in 4 (6.5%) children.

Most frequently identified food allergens included cow milk proteins, hen egg white, soya protein, fish protein and oranges. Grass pollen, tree pollen, bush and weed pollen, house dust mites and cat fur were the most common inhalatory allergens.

Elevated serum relative eosinophilia in peripheral blood

within the range of values >5-8% was observed in 24 patients (38.8%) from group 3 and in 5 (6.5%) from group 2.

Relative eosinophilia in the range of values >8-15% was found in 18 (29.0%) children from group 3.

Atopy (positive family history of allergy and elevated serum tIgE) was diagnosed most frequently in 25 children with secondary GER (40.3%) from group 3, being the least common in group 2 children with primary GER (3; 3.9%).

Discussion

Allergy to cow milk protein or to other food products in children, irrespective of their age, is one of the more frequently recognized causes of secondary GER, although so far this relationship has been rarely described in clinical reports [10,24,25,27].

The first and fundamental step in making a decision about antireflux treatment is differentiation between primary (idiopathic) GER and secondary (to food hypersensitivity) GER. To do this we implemented our own algorithm of diagnostic-therapeutic procedure [9,16,26,28-31].

As revealed by our observations and clinical investigations performed on a relatively large group of infants in the first year of age, cow milk allergy (CMA) is the cause of secondary GER in 43% of cases [12]. These investigations also confirm that the application of cow milk elimination diet considerably improves clinical condition of children with CMA and GER; thus, the coexistence of these two pathologic entities is not coincidental [12].

Our findings have been confirmed by the results published by the Italian researchers who found secondary GER in infants with CMA in 16-40% of cases [8,10,32].

In a group of vomiting infants, Staiano et al. revealed pathologic GER coexisting with CMA in 16% and CMA alone in the same percentage of cases [8].

Cavataio et al., in prospective studies, found coexistence of CMA and GER in 41.7% [10,32].

At the same time, these authors did not reveal any significant differences in age, gender or clinical picture between children with primary and secondary GER.

In the current study, conducted on a group of children at various age, the share of cow milk and/or other food allergy in initiation of secondary GER was estimated at 36.5%, accounting for 44.9% in gastroesophageal reflux disease (GERD). Clinical manifestation (type of reflux symptoms, mono- or polysystemic, frequency in isolated or associated form) in children with GER secondary to CMA/FA showed no significant differences as compared to that observed in primary GER.

However, it should be emphasized that 37% of children with both CMA/FA and GER developed typical allergic symptoms, such as generalized dermatitis, urticaria, rhinitis, itching of the skin, chronic diarrhea.

Obviously, the children with CMA/FA showing remission of secondary GER following elimination diet should undergo oral challenge test with cow milk and/or another harmful food product (open or blind according to the patient's age and types of clinical symptoms) to confirm the cause-and-effect relationship between these two pathologic conditions [26,30].

However, a positive family history of allergic diseases, clinical evidence of allergy, i.e. its constitutional features, allergologic and immunologic tests and their proper interpretation appear to be very useful and helpful in establishing definite diagnosis and confirming the allergic cause of detected GER in children [2,9,12,13,25,26,33].

Conclusions

1. Coexistence of cow milk allergy and food allergy (CMA/FA) with esophageal reflux disease was found in 44.9% of children at various age.

2. Clinical symptoms caused by acid GER associated with CMA/FA (secondary), irrespective of age, are nonspecific and similar to or identical with those observed in primary acid GER.

3. Commonly available and accepted allergologic and immunologic tests should be used to confirm or exclude the relationship between GER and CMA/FA in children; positive results indicate IgE-dependent pathogenetic mechanism underlying clinical symptoms. However, it is the positive food challenge that is a decisive test.

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