Is acid gastroesophageal reflux in children with ALTE etiopathogenetic factor of life threatening symptoms?

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Abstract

Purpose: Commonly described multiorgan manifestation of acid GER: primary and secondary to cow's milk allergy and/or other food (CMA/FA) sometimes coexists with ALTE (Apparent Life Threatening Events) syndrome symptoms. Among these symptoms are apnea, cyanosis, pallor, hypotonia, non-epileptic seizures, consciousness disorders and bradycardia.

Materials and methods: 264 children aged: 4-102 months (x=20.78±17.23 months) of both sexes, with symptoms suggestive of GER were enrolled into study. 8 children (4.8%) aged up to 2 years (x=10.00±2.78 months) of both sexes with symptoms suggestive of ALTE were selected from the group. 24-hour esophageal pH monitoring was used for acid GER diagnosis in these children.

X-ray of esophagus with barium swallow was performed in order to evaluate the height of GER in infants. Immunoallergologic tests were performed in order to differentiate acid GER: primary and secondary to food allergy in these children.

Aims: 1. Assessment of the prevalence of acid GER in children with symptoms suggestive of ALTE,

2. Clinical evaluation of symptoms in children with ALTE and acid GER,

3. Assessment of efficacy of conservative treatment in children with reflux and ALTE symptoms,

4. Natural regression of the disease in children with ALTE

Results: From among 264 examined children who underwent 24-hour esophageal pH monitoring acid GER was confirmed in 170 (64.4%), and ALTE in 8 (4.8%). The causative role of primary acid GER in children with ALTE regarded to 4 children (50.0%) and GER secondary concerned 4 remaining children (50.0%). Mean number of ALTE episodes that appeared before admission to the hospital was similar in both study groups. The presence of typical reflux symptoms in 5 (62.5%) out of 8 children with ALTE symptoms on the basis of primary or secondary acid GER is significant. Mean value of total acid GER index in a subgroup of children with primary GER constituted x=11.13±1.45 and was not statistically significant in comparison with mean value x=12.13±1.30 of a parameter measured in a subgroup of children with secondary GER. The most common clinical manifestation was apnea and it was of identical prevalence in both study subgroups. Analysis of clinical differentiation of the course of ALTE in children with primary and secondary acid GER under conservative therapy was performed. Under this therapy, gradual regression of ALTE symptoms was achieved in all (8/100.0%) patients, with a tendency to longer time of improvement in children with secondary GER. Typical and atypical symptoms of GER receded in a subgroup with primary GER and were alleviated in a subgroup with secondary GER. In the second half year of clinical observation aggravation of reflux and ALTE symptoms was observed in subgroups. In the second year of clinical observation various typical and atypical symptoms of GER were observed in both subgroups. All these malaises during this period coexisted with ALTE symptoms. In the third year of clinical observation in both subgroups ALTE symptoms connected with acid GER were not observed.

Conclusion: Primary and secondary GER were defined as the causative factors of ALTE in 8 (4.8%) examined infants.

Key words: Acid GER, ALTE, food allergy, infants, youngest children.

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Table 1. **Research methods (by Wasilewska et al.) [17]**

Basic laboratory tests	Standard diagnostic procedures
1. laboratory parameters of inflammation	1. medical history
2. bacteriological examination	2. clinical examination (disorders)
3. titer of antiviral antibodies	3. cardiological examination + ECG/ ECHO
4. laboratory biochemical-metabolic screening	4. neurological examination + EEG
5. acid-base balance parameters (i.e. partial pressure of O_2 and CO_2, blood saturation)	5. ophthalmological examination
6. chest X-ray postero-anterior and lateran	6. ultrasound scan of abdominal cavity (esophageal gastric junction)
	7. transfontanellar ultrasound scan
	8. 24-hour intraesophageal pH monitoring
	9. X-ray of upper gastrointestinal tract with barium swallow
	10. immunoallergological examination (skin tests with food and inhalant allergens i.e. Prick tests, total and specific IgE, oral food challenge test
	11. polysomnography – not performed due to lack of informed parental consent or psychomotoric hypersensitivity in these children

Introduction

Acid gastroesophageal reflux (GER) in infants and children has various clinical manifestation. Commonly described multiorgan manifestation of GER is sometimes accompanied by life threatening symptoms defined as ALTE syndrome (Apparent Life Threatening Events). The most typical symptoms of ALTE syndrome are: breathing disorders (apnea); with apnea or independent of it: change in skin colour (cyanosis or pallor), muscle tension disorders (hypotonia or non-epileptic seizures), gagging, choking and salivation, consciousness disorders and arrhythmias (bradycardia) [1-8]. Intensity of these symptoms may be variable and symptoms may recede spontaneously or as a result of administered treatment. These symptoms are nonspecific and may appear in many other disorders during childhood, i.e. infections or metabolic, neurological, cardiovascular disorders etc. Diagnosis of ALTE syndrome requires differential diagnosis due to various causes of the syndrome [2,9].

Acid GER is considered to be one of the causes of ALTE. However, opinions on coexistence of symptoms and etiopathogenetic interconnections between these disorders are still divergent [10-14]. Also food allergy, especially cow's milk allergy could be a causative factor of GER (secondary GER) but hardly ever a direct cause of general ailments described in the course of ALTE [15,16].

Aims of the study

1. Assessment of the prevalence of acid GER in children suspected of ALTE,

2. Clinical evaluation of symptoms in children with ALTE and acid GER,

3. Assessment of efficacy of conservative treatment in children with reflux and ALTE symptoms,

4. Natural regression of the disease in children with ALTE and coexistent GER (3-year clinical observation).

Materials and methods

264 children aged 4 to 102 months (mean age x=20.78±17.23 months), of both sexes with symptoms suggestive of gastroesophageal reflux (GER) were enrolled in a study. These children were admitted to the III Department of Pediatrics of the Medical University of Bialystok. A subgroup of 8 children up to 2 years of age (mean age x=10.00±2.78 months), of both sexes with symptoms suggesting ALTE was selected. Diagnosis of ALTE was determined on a basis of differential diagnosis (*Tab. 1*), excluding infections of respiratory tract/urinary tract/digestive tract etc., infections (bacterial/viral), neurological disorders, cardiovascular disorders/anomalies, metabolic disorders (lactic acidosis, with or without hypercholesterolemia), adverse drug and food reactions [17].

24-hour esophageal pH monitoring was used for diagnosis of GER. The result of the examination was always related to clinical manifestation of the disease in examined children. The following parameters of pH monitoring were examined: the number of acid GER episodes (intraesophageal pH below 4.0), the number of acid GER episodes lasting more than 5 minutes, total acid GER index (RI), i.e. percentage of time with intraesophageal pH below 4.0.

Qualitative and quantitative evaluation of gastroesophageal reflux was performed together with the basic pH parameter i.e. total acid GER index (RI) – percentage of time with pH below 4.0 (%).

The results of esophageal pH monitoring in infants were related to borderline values collected by Vandenplas, et al. [18-20]. The borderline value for total acid GER index was ≤9%.

A chest X-ray with barium swallow was performed in order to rule out anatomical anomalies of the upper gastrointestinal tract, sometimes coexisting with tracheal, bronchial or diaphragm disorders and to establish height of GER in infants.

The range of GER was defined on the basis of Mc Cauley Grading System of the intensity of reflux [21].

The diagnostic and therapeutic algorithm was used in order to differentiate primary GER and GER secondary to cow's milk allergy and/or other food (CMA/FA) in these children [9].

This algorithm includes results of immunoallergologic tests, i.e. skin tests with food and inhalant allergens (Prick tests), total serum IgE and specific IgE, peripheral blood eosi-

***Table 2*. Analysis of selected children with ALTE and acid GER: primary and secondary to food allergy (FA)**

Children with ALTE	Total	Children with primary GER	Children with secondary GER
Number of children	8	4	4
Sex: girls/boys	3/5	1/3	2/2
Age at diagnosis (months; mean value)*	10.00±2.78	12.00±2.58*	8.00±0.82*
Gestational age (weeks; mean value)	36.7	36.0	37.0
Body mass at birth (grams; mean value)	2760	2820	2700
Pregnancy pathology/perilabour period	3/8	1/4	2/4
Presence of reflux symptoms (vomiting, regurgitation)	5/8	3/4	2/4
ALTE (mean no. of episodes before hospital admission)	3.5	3.25	3.75
Abnormalities in physical examination (at hospital admission, after ALTE episode)	4/8	0/4	4/4

* p=0.03

nophilia and oral food challenge test with a potentially noxious nutrient [9,22,23].

In children up to 2 years of age an open provocative test with cow's milk and/or other noxious nutrient (determined with the help of medical history) were performed [22].

Information about the ALTE episodes gathered from parents was compared with the type and intensity of reflux symptoms according to the agreed score system (scope 1-4 pts):

1 – symptoms of mild intensity occurring episodically

2 – symptoms of moderate intensity occurring episodically

3 – symptoms of considerable intensity occurring episodically

4 – symptoms of high intensity occurring daily.

Patients with reflux symptoms of variable degree of manifestation required temporary (few days) or periodically repeated (4-6 weeks) treatment; and they were taken under constant clinical care. The aim of this procedure was to establish the efficacy of treatment and prevention of recurrence of ALTE episodes.

In order to diagnose pathological primary and secondary acid GER in examined children 2 versions of comprehensive treatment were administered [16,24-26]:

1) antireflux treatment exclusively (in children with primary GER)

a) Stage I – positional treatment (postural) + antacids and protective drugs + parental education,

b) Stage II – Stage I + prokinetics,

c) Stage III – Stage II + histaminic receptor (H2) antagonists and/or proton pomp inhibitors;

2) combined treatment – antiallergic and antireflux (in children with GER secondary to food allergy)

a) variant I – antiallergic treatment (dietetic treatment – elimination diet, antiallergic treatment) and antireflux treatment (Stage I),

b) variant II – antiallergic and antireflux treatment (Stage II or III).

Duration of treatment was dependent on the clinical manifestation and the degree of intensity of the disease and also on the efficacy of the treatment implemented. Efficacy of exclusive antireflux treatment or combined treatment was assessed on the basis of the intensity of symptoms (resolution or alleviation). Esophageal pH monitoring or oral food challenge test (GER secondary to food allergy) were performed periodically to verify diagnosis of acid GER.

In order to standardize the assessment of treatment efficacy the following agreed classification has been implemented:

resolution of symptoms	(Res)
alleviation of symptoms=improvement	(I)
no improvement	(NI)
aggravation	(A)
symptoms of variable intensity, appearing periodically = recurrences	(Rec)

The study was approved by local Bioethical Committee of the Medical University of Białystok and informed parental consent was obtained from parents of examined children.

Any statistical comparison was not reliable consequent upon insufficient number of children with ALTE syndrome examined in both subgroups.

Results

Among 264 examined children 24-hour esophageal pH monitoring confirmed pathological acid GER in 170 (64.4%) and ALTE in 8 (4.8%). Simultaneously upper gastrointestinal X-ray with barium swallow was performed in children with ALTE symptoms which confirmed high reflux. The causative role of primary acid GER in ALTE was confirmed in 4 children (50.0%) and GER secondary to cow's milk allergy in remaining 4 children (50.0%). The analysis of selected children with ALTE and primary and secondary GER is presented in *Tab. 2*. Presentation of age differentiation (statistically significant; p=0.03) between both subgroups at diagnosis seemed to be important. Children with primary GER were older than children with GER secondary to CMA/FA. Mean number of ALTE episodes that occurred before hospital admission was comparable in both study groups.

Clinical manifestation of the disease revealed typical reflux symptoms in 5 children (62.5%) and lack of these symptoms in 3 (37.5%) out of 8 children with ALTE symptoms on the basis of primary or secondary GER. Mean number of ALTE episodes that occurred before hospital admission was comparable in both study groups. Typical reflux symptoms in 5 (62.5%) and lack of these symptoms in 3 (37.5%) children out of 8 with ALTE symptoms on the basis of primary or secondary GER are highly significant. The clinical examination of children with symptoms of ALTE

***Table 3*. Comparative analysis of the results of tests confirming acid GER in examined children with ALTE**

Examinations confirming acid GER in children with ALTE							
24-hour intraesophageal pH monitoring Percentage of time with pH<4.0 (total GER index %)				X-ray of upper gastrointestinal tract Mc Cauley classification of grading [21]			
Inicials	Children with primary GER	Inicials	Children with secondary GER	Inicials	Children with primary GER	Inicials	Children with secondary GER
K.P.	9.7	K.K.	10.3	K.P.	III^0	K.K.	IV^0
B.J.	11.2	B.M.	12.5	B.J.	III^0	B.M.	IV^0
L.A.	10.5	S.G.	12.3	L.A.	IV^0	S.G.	III/IV^0
A.W.	13.1	M.M.	13.4	A.W.	III^0/IV^0	M.M.	IV^0
X	11.125±1.45	X	12.125±1.30	X	3.37±0.48	X	3.87±0.25
p=ns				p=ns			

***Table 4*. Analysis of clinical manifestation of ALTE in children with acid GER: primary and secondary to food allergy (FA)**

Clinical manifestation of ALTE in examined children	Children examined – total [N=8]	Type of disorder	
		Primary GER [N=4]	Secondary GER [N=4]
Apnea	8	4	4
Consciousness disorder	6	2	4
Hypotonia	5	2	3
Pallor	4	1	3
Cyanosis	3	1	2
Bradycardia	2	1	1
Non-epileptic seizures	1	-	1

and GER did not reveal any anomalies after ALTE episode. Confirmation of diagnosis of acid GER and assessment of its range in examined children with ALTE are presented in *Tab. 3*.

Pathologic acid GER was diagnosed on the basis of values of total acid GER index registered. Mean value of this parameter obtained in a subgroup of children with primary GER was x=11.13±1.45 and was lower than mean value of the examined parameter obtained in a subgroup of children with GER secondary to CMA/FA x=12.13±1.30 (difference not statistically significant). The range of GER in selected children was considered high due to approved radiological Mc Cauley's classification [21].

Mean value of height degree of barium reflux in a subgroup of children with primary GER was x=3.37±0.48 and was lower than a mean value of reflux in a subgroup of children with GER secondary to CMA/FA x=3.87±0.25 (difference not statistically significant).

Clinical manifestation of ALTE in children with primary and secondary GER (*Tab. 4*) revealed that the most common symptom was apnea appearing with the same prevalence in both study groups. Relatively less common were consciousness disorder, hypotonia, pallor, cyanosis – and these were more common in a subgroup with secondary GER, whereas bradycardia was a very rare symptom in both study groups. Similarly non-epileptic seizures were observed exclusively in a subgroup with secondary GER.

Symptoms aforementioned, which are typical for ALTE, were predominant in a subgroup of the youngest children with secondary GER. In a subgroup of children with secondary GER, ALTE symptoms were accompanied by allergy symptoms: skin lesions, mucous lesions in oral cavity (aphthae), rhinitis, chronic diarrhoea with mucus or eosinophilia in faeces.

Characteristics of clinical manifestation in children with ALTE and GER at admission to hospital (diagnosis, medical history) is presented in *Tab. 5*.

The prevalence of typical reflux symptoms was demonstrated in 5 children (62.5%) and such symptoms were not observed in 3 children (37.5%) with acid GER who had atypical clinical manifestation. All these ailments appeared in combination with ALTE symptoms. Among typical reflux symptoms vomiting was more intense in a subgroup of children with secondary GER and regurgitation prevailed in a subgroup of children with primary GER.

The less common symptoms were: food refusal, swallowing and belching in children with secondary acid GER and failure to thrive and choking in children with primary GER.

Among the atypical symptoms of reflux (out of gastrointestinal tract) anxiety and postprandial crying and/or night cough and coryza were observed in children with secondary GER, and anxiety and/or crying during day and night sleep only in 1 child with primary GER.

Analysis of clinical differentiation of the course of ALTE in children with primary GER and GER secondary to CMA/FA under administered treatment was performed. Two endpoints were taken into account: the time of basic treatment completion and the first year of 3-year-clinical observation (*Tab. 6*).

Two types of treatment were administered: antireflux treatment and combined treatment – antiallergic and antireflux. The time of antireflux treatment in a subgroup of children with primary GER lasted from 6 up to 24 weeks (mean time x=15.0±7.75) and was shorter than combined treatment in children with secondary GER which lasted 12 to 36 weeks (mean time x=21.0±11.49), (difference statistically not significant). Gradual resolution of ALTE symptoms was achieved in all children (8/100.0%), with a tendency to longer period of obtaining it in children with sec-

***Table 5*. Clinical symptoms of ALTE (data from patients' medical history) in children with acid GER: primary and secondary to food allergy (FA) – at diagnosis**

Children with ALTE					Clinical manifestation of ALTE						
No	Age at diagnosis (months)	Sex	Cause	Clinical symptoms of GER	Apnea	Consciousness disorder	Hypotonia	Pallor	Cyanosis	Bradycardia	Non-epileptic seizures
1.	7	M [♂]	Secondary GER	vomiting 2-3 x per day, swallowing, food refusal	+	+	+	+	-	-	-
2.	8	F [♀]		anxiety/postprandial crying, food refusal	+	+	+	+	+	-	-
3.	8	M [♂]		swallowing, anxiety and night cough.	+	+	+	+	-	-	-
4.	9	F [♀]		vomiting 3-4 x per day, belching, appetite loss, coryza.	+	+	-	-	+	+	+
5.	9	M [♂]	Primary GER	regurgitation 5-6 x per day/vomiting 2-3 x per day	+	-	+	+	-	-	-
6.	11	M [♂]		regurgitation/choking 3-5 x per day	+	-	-	-	+	-	-
7.	13	F [♀]		regurgitation/vomiting 2-3 x per day, failure to thrive	+	+	-	-	-	+	-
8.	15	M [♂]		anxiety/crying during sleep every day	+	+	+	-	-	-	-

***Table 6*. Clinical observation of children with acid GER and ALTE (1st year after the completion of treatment)**

Children with ALTE															
No.	Age at diagnosis (months)	Cause	Conservative treatment				Age after treatment (months)		Assessment of treatment efficacy in the 1st year after treatment completion (weeks)					
			Antireflux		Combined				0-6	6-12	13-24	25-36	37-48	
			receiving/ not receiving	Duration (weeks)	receiving/ not receivng	Duration (weeks)								
1.	7	GER secondary to FA	-	-	+	12	10	x=13.2±3.6	Rec(2)	I(1)	Res	Rec(2)	I(1)	Res
2.	8		-	-	+	24	14		Rec(2)	NI(2)	I(1)	A(4)	Res	Rec(2)
3.	8		-	-	+	12	11		Res	Res	Rec(3)	I(2)	I(1)	Res
4.	9		-	-	+	36	18		Rec(2)	NI(2)	A(4)	I(3)	I(1)	
5.	9	Primary GER	+	6	-	-	10.5	x=16.0±4.3	Res	Res	Rec(2)	NI(2)	I(1)	Res
6.	11		+	18	-	-	15.5		Res	Res	Rec(3)	I(2)	A(4)	Res
7.	13		+	12	-	-	17		Res	Res	Res	Rec(2)	NI(2)	Res
8.	15		+	24	-	-	21		Rec(2)	I(1)	A(3)	NI(3)	I(1)	

x=15.0±7.75

x=21.0±11.49

ondary GER. However, regression of typical and atypical reflux symptoms was observed in 4 children with primary GER and their significant alleviation in 4 children with secondary GER.

The efficacy of administered treatment was assessed after first year of observation and longer time of absence of reflux ailments and ALTE symptoms (first 6 months: 12-24 weeks) was revealed in a subgroup of children with primary GER, in comparison with a subgroup of children with secondary GER. At that time the lack of clinical recovery or a tendency to recurrence of symptoms was observed in the discussed group.

In the second half year (25-48 weeks) of clinical observation the intensification of clinical manifestation of reflux symptoms and ALTE was observed in children of both subgroups. These children required periodical intensive treatment.The assessment of clinical examination of children with primary and secondary acid GER in a consecutive years of clinical observation are presented in *Tab. 7* (Part I and II).

In the second year of clinical observation paroxysmal abdominal pain, vomiting, and saliva swallowing were observed among typical reflux symptoms. Less common were regurgitation and belching appearing in a subgroup of children with secondary GER.

Table 7. Further clinical observation of children with acid GER and ALTE syndrome (following years). Part I.

Children with acid GER and ALTE									
No.	Age after 1 year of clinical observation (months)	Cause	2nd year of clinical observation		Age after 2 years of clinical observation (months)	3rd year of clinical observation		Age after 3 years of clinical observation (months)	
			Reflux symptoms	ALTE symptoms		Reflux symptoms	ALTE symptoms		
1.	22	GER secondary to FA	Rec vomiting 1-2 x per day and abdominal pains – 2-3 days (4 episodes every 5-6 days)	Rec apnea, pallor, hypotonia and consciousness disorder 2 episodes every 5-6 days (after 8 days of open provocation test to cow's milk)	34	Rec swallowing, hiccough, morning bad breath – 14-21 days (2 episodes every 12-18 weeks)	Res	46	
2.	26	GER secondary to FA	Rec vomiting/regurgitation, swallowing, hawking 2-3 x per day – 3-4 days (6 episodes every 10-14 days)	Rec apnea, pallor, hypotonia and consciousness disorder (3 episodes every 14 days)	38	Rec hawking and hoarsness lasting 3-4 weeks, receding after combined treatment (3 episodes every 5-7 weeks)	Res	50	x=49.25±3.59
3.	23	GER secondary to FA	Rec night cough and wheezing breath; hoarsness – 2-3 weeks (4 episodes every 4-6 weeks)	Rec apnea, short-term (≤1min.) consciousness disorder, pallor, hypotonia, and excessive salivation (5 episodes every 4-6 weeks)	35	Rec night and postprandial cough, hoarsness lasting 2-3 weeks (3 episodes every 8-9 weeks)	Res	47	
4.	30	GER secondary to FA	Rec paroxysmal abdominal pains, belching and swallowing – 10-14 days (3 episodes every 4-6 weeks)	Rec apnea, cyanosis, consciousness disorder and non-epileptic seizures (2 episodes)	42	Rec pain/heartburn, hoarsness after night and hawking – 5-7 days (3 episodes every 4-10 weeks)	Res	54	
	x=25.25±3.59				x=37.25±3.59				

Table 7. **Further clinical observation of children with acid GER and ALTE syndrome (following years). Part II**

Children with acid GER and ALTE									
No.	Age after 1 year of clinical observation (months)	Cause	2nd year of clinical observation		Age after 2 years of clinical observation (months)	3rd year of clinical observation		Age after 3 years of clinical observation (months)	
			Reflux symptoms	ALTE symptoms		Reflux symptoms	ALTE symptoms		
5.	22	Primary GER	Rec regurgitation 3-5x per day, anxiety/crying during sleep and feeding – 5-8 days (3 episodes every 4- 5 weeks)	Rec apnea, hypotonia, pallor (3 episodes every 4-5 weeks)	34	Res	Res	46.5	
6.	27	Primary GER	Rec belching and swallowing 3-4 x per day, lasting 3-4 weeks (2 episodes every 4-5 weeks)	Rec apnea and cyanosis at exacerbation of reflux symptoms (2 episodes)	39.5	Res	Res	51.5	x= 52.00±4.33
7.	29	Primary GER	A vomiting 1-2 x per day, regurgitation and heartburn – 10-14 days (3 episodes every 8-10 weeks)	Rec apnea and bradycardia at exacerbation of reflux symptoms (1 episode)	21	Res	Res	53	
8.	33	Primary GER	Rec vomiting, anxiety/postprandial and during sleep crying, appetite loss – 2 weeks (4 episodes every 7-8 weeks)	Rec apnea, hypotonia and consciousness disorder at exacerbation of reflux symptoms (2 episodes)	45	Rec abdominal pain, chronic hoarsness and appetite loss, lasting 7-10 days (4 episodes every 4-6 weeks)	Res	57	
	x=27.75±4.57				x=34.87±10.28				

In a subgroup of children with primary GER vomiting and regurgitation, and also occasional swallowing, belching, regurgitation of stomach contents into the esophagus and heartburn or appetite loss should be mentioned. Atypical symptoms such as night cough, wheezing breath, hoarsness, and hawking were observed with a similar prevalence in 2 children with secondary GER, whereas anxiety and/or crying during feeding and during sleep in 2 children with primary GER. All these ailments still coexisted with ALTE symptoms during the period of clinical observation.

In children with secondary GER apnea with short consciousness disorder (≤1 min.) was a dominant symptom, whereas pallor and hypotonia were less common and cyanosis and non-epileptic seizures appeared occasionally. In all children with primary GER apnea with other occasional ALTE symptoms such as hypotonia, pallor or cyanosis, bradycardia or consciousness disorders were observed. After 2 years of clinical observation mean age of children with GER secondary to CMA/FA was x=37.25 months ±3.59 and was not statistically significant with regard to mean age of children with primary GER which accounted for x=34.87 months ±10.28. In the third year of clinical observation no ALTE symptoms connected with acid GER were observed in both study subgroups of children with primary and secondary GER. Foetor ex ore, saliva swallowing, abdominal pain and heartburn were observed among typical reflux symptoms of similar prevalence in children with secondary GER. Within atypical reflux hoarsness was a dominant symptom, and hawking, night and/or postprandial cough were less common.

In the third year of clinical observation in a subgroup of children with primary GER periodical abdominal pains, appetite loss and hoarsness of recurrent character were observed in 1 child only. At the completion of 3-year clinical observation mean age of children with secondary GER was x=49.25 months ±3.59 and was similar to mean age of children with primary GER which was x=52.00 months ±4.33 (not statistically significant).

Discussion

In 3-year clinical observation chronic or recurrent reflux and/or ALTE symptoms of variable intensity were observed especially in children with secondary GER, regardless of periodically administered treatment. This tendency was presumably the result of aggravation of gastrointestinal allergy to various allergens (food or inhalant) [16,24,25].

To prove cause-and-effect relationship between acid GER symptoms and ALTE episodes it is required to perform 24-hour esophageal pH monitoring and assess function of the following systems: nervous system, respiratory and cardiovascular system. It is also necessary to prove that ALTE symptoms remain with the time correlation with inappropriate acid esophageal pH<4.0. Nevertheless, these correlations have not been reliably proved in a clinical practice yet.

Nowadays polysomnography is used instead of standard esophageal pH monitoring [14,27]. On the basis of implemented antireflux treatment or combined treatment these correlations can be indirectly presupposed. Simultaneous registration of esophageal pH and polysomnography in the youngest healthy children showed that acid GER is a physiological process in this group, especially intense in a REM (rapid eye movement) phase of sleep [14]. As a physiological process it does not trigger of symptoms of a disease but may be the cause of awakenings of the youngest children. Together with age and development of nervous system and sleep-vigil cycle, and reduction of percentage of REM phase, physiological acid GER gradually decreases [14,27].

Only older infants with acid GER proved with pH monitoring were enrolled in a study.

Therefore divergent opinions on the ethiopathogenesis of ALTE with acid GER could at least partially be the effect of different methods of the performed examinations.

Crucial methodological suggestion could be performance of 24-hour intraesophageal pH-monitoring, which is a standard diagnostic procedure in acid GER in children with ALTE symptoms [18-20].

Kahn et al. did not show the time relationship between episodes of drop in pH in esophagus and apnea and bradycardia in infants with ALTE [13]. However, in the discussion part of the study the possibility of obtaining false negative results due to reflux of gastric contents of low acidity (pH>4.0) or neutral (pH=5-7) is mentioned, which may appear especially after feeding and is not reliably registered by pH monitoring probe [13].

There is also lack of unambiguous confirmation of time relationship between pH drop in esophagus and symptoms of reflux and ALTE in the youngest children, in both subgroups. On the other hand the time relationship between the onset of reflux symptoms (typical and atypical) and apnea and consciousness disorder, and other ALTE symptoms, usually within 30 up to 60 minutes after feeding and/or in a supine position, during sleep was proved in a clinical practice.

Taking into consideration methodological representations aforementioned, these authors do not exclude the existence of acid GER in children with ALTE especially in infants with obstructive apnea during sleep. In case of doubts they suggest administration of antireflux treatment as a verifying diagnostic and therapeutic test [13].

Significant methodological recommendation should be 24-hour intraesophageal pH monitoring approved as a standard procedure in a diagnosis of acid GER in children with ALTE [17-20].

Graff et al. showed uselessness of short-term monitoring techniques: 1 hour Tuttle test or 4 hour polisomnographic recording with a simultaneous esophageal pH-registration as a diagnostic method of acid GER in infants with ALTE [10]. Sensitivity of these tests with regard to 12 hour monitoring was 55% and 82%, respectively [10].

On the basis of reports aforementioned it could be thought that chest X-ray of upper gastrointestinal tract with barium swallow is not an optimal procedure in diagnosis of GER [10].

This procedure was performed in own studies in the youngest children, in order to rule out anatomical anomalies of this part of gastrointestinal tract and at the same time to assess the height of regurgitation of gastric contents into esophagus.

The presence of symptoms from the gastrointestinal tract

typical for acid GER (vomiting, regurgitation, etc.), which were present in 62.5% examined children supports the necessity of reflux diagnostics, regardless of the absence of abnormalities in clinical examination after ALTE episode.

Despite the fact that 24-hour esophageal pH monitoring has been considered as the diagnostic gold standard, it only enables to reveal changes of pH<4.0, i.e. acid GER. This procedure does not allow to discover non-acid GER, in which pH of esophageal contents is between >4-6.8 (neutral pH) or above 7.0 (alkaline bile GER) [18-20,28].

The reliable diagnostic method is electric impedance measurement (Multichannel Intraluminal Impedance – MII) combined with pH-monitoring enabling to diagnose reflux regardless of pH (acid and non-acid GER) [29].

The prevalence of recurrent vomiting or regurgitation in children with ALTE syndrome constitutes 60-70%, and at the same time in 40-80% of cases inappropriate pH monitoring recording is ascertained.

Clinical reports regard ALTE episodes that are triggered of by backward food movement into oral part of pharynx or aspiration of gastric contents.

Intense vomiting or regurgitation correlated with prolonged apneas (>20 sec.) and also with shorter apneas connected with bradycardia, but majority of long lasting apneas was connected with regurgitation in these patients [1,2,27].

Studies regarding simultaneous esophageal pH monitoring, heart rate, chest movements and nasal flow showed that GER could precede apnea [2,27,30].

In selected children who experienced ALTE episodes it was proved that hydrochloric acid infusion into esophagus triggers of obstructive apnea or reducing blood saturation, which suggests that ALTE episodes on the basis of acid GER may appear due to stimulation of chemoreceptors of pharynx, esophagus and larynx with subsequent contraction [2,3,7].

Despite previous reports that GER may lead to apnea, examinations of children after ALTE episode did not prove actual time correlation between esophagus acidity and apnea or bradycardia [2,3,7,31].

With few studies presenting occasional correlation between acid GER with short-term mixed central apneas (5-15 sec.), in all those patients apneas with no correlation with GER were observed, which could suggest primary disorder of breathing regulation [2,3,7,31].

The most convincing cause-and-effect relationship between GER an apnea episodes on the mixed basis or due to defect of respiratory tract permeability was shown in infants, who experienced those apneas during vigil phase in a supine position and during the first hour after feeding [29,30]. This interdependence can be confirmed with polisomnography. At the same time the lack of evidence that ALTE episode and polisomnography results enable anticipation which infant is at risk of ALTE episode in the future [27,30,31].

In patients with frequent ALTE episodes, with uncertain role of GER, 24-hour esophageal pH monitoring may facilitate determination of time correlation between acid GER and ALTE. In order to provide proper interpretation of the 24-hour esophageal pH monitoring, registration of heart rate, chest impedance, nasal flow and oxygen saturation should be performed simultaneously, which together enable to observe apnea as a result of respiratory tract obstruction (polysomnography recording, electroencephalography recording) [27,30].

Some evidence suggest that better response to antiallergic treatment and/or antireflux treatment may be observed in infants with ALTE and GER of different ethiology in the case of very intense vomiting or regurgitation at ALTE episode and if the episode occurs while child is awake or manifests as obstructive apnea [25,32,33].

In order to reduce the intensity of vomiting and to inhibit acid GER it is advisable to opt out classical method of antireflux treatment [26].

Combined antiallergic and antireflux treatment are taken into consideration only in the case of inefficacy of previous treatment and also if the allergic pathogenesis of antireflux and ALTE symptoms of severe course is confirmed [16,24,25,33]. The comparison of efficacy of both treatments was performed in own studies.

Conclusions

1. Both primary and secondary acid GER have been recognized as causative factors of ALTE in 8 examined children (4.8%).

2. The results obtained justify the necessity of implementation of 24-hour esophageal pH monitoring and immunoallergologic test or polisomnography in diagnostic procedure in children with ALTE syndromes.

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