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Acid Gastroesophageal Reflux Disease and Apparent Life-Threatening Events: Simultaneous pH-metry and Cardiorespiratory Monitoring

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Aim: To investigate the prevalence and the characteristics of gastroesophageal reflux disease (GERD) in infants with apparent life threatening events (ALTE).
Materials and methods: Infants with at least one episode of ALTE in absence of predisposing factors were included. All infants underwent a cardiorespiratory recording with simultaneous 24-hour pH-monitoring. Patients were divided into 3 groups according to the severity of GERD: A. Reflux Index (RI) <3%, B. RI = 3—7%, C. RI >7%. Monthly evaluations were performed and the anti-reflux therapy was maintained till normalization of monitoring and clinic.
Results: 41 infants were enrolled. GERD was found in 80% of patients (moderate in 54%, severe in 27%). A normalization of the cardiorespiratory tracks was recorded on average after 1 month for group A, 7 months for the group B and 9.5 months for group C. A significant difference was registered between group A and both group B and C ($P < 0.0001$), as well as between the group B and C ($P < 0.05$).
Conclusion: GERD influences significantly the time of normalization of the cardiorespiratory monitoring in infants with ALTE. GERD diagnosis and treatment are mandatory in these patients.
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1. Introduction

Apparent life-threatening event (ALTE), previously called near-miss sudden infant death syndrome (SIDS), is "an episode that is frightening to the observer and characterized by a combination of apnea, color change (cyanosis or pallor), marked change in muscle tone, choking or gagging," according to a National Institute of Health consensus conference.[1] The hypothesis that apnea may precede SIDS has led to an extensive development of apnea monitors for domiciliary use.[2] Gastroesophageal reflux disease (GERD) has been considered to play a role in the pathogenesis of ALTE,[3,4] even if previous studies have not been able to demonstrate this relationship.[5,6]

The aim of our study was to investigate the prevalence and the characteristics of GERD in infants with ALTE. In particular, the focus was on the potential influence of GERD on the time of normalization of symptoms and monitoring.

2. Methods

From June 2013 to December 2014, all infants with at least one episode of ALTE and typical symptoms of GERD that were referred to our Center were considered for the present study. After completing a protocol of investigations (Table 1), patients with severe prematurity (<25 weeks gestational age), and any kind of infectious or neurological, cardiac, or metabolic disorders, were excluded.[7] A cardiorespiratory recording was always performed within at least 2 days from the event for a minimal duration of 48 hours. The recording consisted of an airflow monitoring by thermistor to diagnose obstructive apnea, and a monitoring of the heart rate and chest movements by impedance and pulse oximeter. The signals were digitalized and recorded at a rate of four samples per second and downloaded onto a personal computer when completed. Tracings were analyzed using a semiautomated system and reviewed by a technician. Apneas longer than 16 seconds were recorded, as well as the occurrence of bradycardia (to <100 beats/min for >5 seconds) or desaturation (to <85% for >10 seconds).[8,9] Following written informed parental consent, a simultaneous 24-h pH monitoring was performed (DIGITRAPPER pH400 Alpine Biomed ApS, Denmark) with a two-channel probe (Versaflex disposable pH catheter Dual

Sensor; 5−10 cm), with the proximal channel positioned at the junction of the mid and lower third of the esophagus, 2.5 cm above the lower esophageal sphincter, and the distal one in the stomach, as confirmed by a chest X-ray.

During recording, infant care was not altered, and breast milk or formula feedings were continued. None of these infants had ever received pharmacological therapy for GERD at the time of the pH-metry.

Gastroesophageal reflux was diagnosed when the esophageal pH fell below 4.0. Reflux was evaluated by the number of individual episodes, the length of each episode, the total duration of reflux, and the percentage of reflux in the study period [reflux index (RI)].[10] RI is usually considered pathological when it exceeds 4%. In order not to underestimate the reflux, we decided to divide the population into three groups: group A, which has a normal RI (<3%); group B, which has a moderate increase in RI (3−7%); and group C, which has a severe increase in RI (>7%; Table 2). Furthermore, the evidence of a pathological monitoring was also determined in the presence of interdigestive episodes of reflux, including prolonged and/or nocturnal ones, and according to the symptom index.

Groups B and C were subsequently treated with proton pump inhibitors (Esomeprazole) at a dosage based on the child's weight (1 mg/kg per day).

The follow-up was characterized by monthly clinical evaluations associated with cardiorespiratory monitoring. Pharmacological antireflux therapy was prolonged until the normalization of the monitoring and the resolution of symptoms. Children were considered cured after two consecutive monitorings within the normal range. Normalization of the cardiorespiratory monitoring was considered when there was no evidence of apnea, bradycardia, or desaturation.

Gestational age at birth, birth weight, and sex were analyzed as potential risk factors for GERD. Patients were divided into two groups according to gestational age: patients born prior to the 30th gestational week and patients born afterward. Considering birth weight, patients were divided into very low birth weight (VLBW; <1500 g) and other than VLBW (>1500 g). The study was granted preliminary approval by our institutional Ethical Committee as part of the institutional protocol for the management of GERD (M.04.360).

2.1. Statistical analysis

Normalization time was compared between groups using one-way analysis of variance followed by Bonferroni method and linear regression analysis. When considering potential risk factors, such as birth weight, gestational age, and sex, statistical analysis was performed with Fisher's exact test. A p value <0.05 was considered statistically significant. StatView software 5.0 was used for the analysis.

3. Results

Fifty infants (28 males, mean age 1.5 months) were referred to our Center during the study period. Clinical manifestations of these infants are shown in Figure 1. Based on the results of the preliminary protocol of investigations,

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Table 1 Protocol of investigation for children with ALTE.

- Recording of anamnesis
- Blood chemistry
- Dosage of serum and urinary amino acids and urinary organic acids
- Cardiac evaluation with ECG and cardiac US (+ Holter registration in case of arrythmias)
- Neurological evaluation with EEG and or polysomnography
- Brain MRI
- 48 h cardiorespiratory monitoring
- 24 h pH-metry

ALTE = apparent life-threatening event; ECG = electrocardiogram; EEG = electroencephalogram; MRI = magnetic resonance imaging; US = ultrasound.

Table 2 Data of the study population.

Patient	Birth weight (g)	Sex	Gestational age (wk)	Symptoms	Age at pH-metry (d)	RI (%)	Group	SI (%)	Normalization of monitoring (no. of evaluations)
1	1430	M	31	Des	75	15.1	C	33	5
2	1750	M	30	Des + apn + cyan	55	5.6	B	43	5
3	2230	F	34	Des + apn + cyan	31	6.7	B	50	7
4	1320	F	27	Des + apn + cyan	70	11.5	C	87	11
5	1250	F	31	Des	80	1.7	A	25	1
6	2580	M	35	Des + apn + cyan	20	5.6	B	55	6
7	1410	M	29	Des + apn + cyan	62	13.7	C	67	10
8	3100	M	38	Des	18	4.5	B	28	6
9	2750	F	37	Des	22	5.7	B	43	8
10	2920	F	38	Des	28	3.5	B	33	4
11	1375	M	28	Des	72	6.6	B	67	7
12	3075	M	39	Des + apn + cyan	33	7.0	B	73	6
13	2490	M	35	Des + apn + cyan	45	8.6	C	60	6
14	1980	F	33	Des	42	0.3	A	33	1
15	1380	M	32	Des + apn + cyan	65	2.1	A	10	1
16	3310	F	39	Des + apn + cyan	35	5.1	B	55	5
17	1680	M	33	Des	66	4.5	B	60	3
18	1120	M	26	Des + apn + cyan	95	14.0	C	50	9
19	2890	M	37	Des + apn + cyan	39	6.6	B	67	3
20	3130	M	38	Des	26	9.0	C	80	7
21	2780	F	37	Des	42	4.3	B	62	9
22	2550	F	36	Des + apn + cyan	45	5.9	B	43	7
23	1235	F	27	Bradi + des	69	16.8	C	50	11
24	3020	F	39	Bradi + des	24	0.2	A	10	1
25	1790	M	34	Des	78	12.8	C	90	8
26	2230	M	35	Des + apn + cyan	60	6.7	B	60	5
27	3180	F	39	Des + apn + cyan	27	6.9	B	67	10
28	2590	M	36	Des + apn + cyan	39	4.0	B	55	2
29	2775	M	37	Des	22	2.5	A	14	1
30	2960	F	37	Des + apn + cyan	15	6.5	B	73	6
31	3310	F	40	Des + apn + cyan	19	2.9	A	20	1
32.	2480	M	35	Des + apn + cyan	40	4.4	B	62	5
33	2660	F	35	Des	44	1.2	A	25	1
34	3150	F	39	Des	28	12.2	C	73	9
35	2820	M	38	Bradi + des	35	7.0	B	75	7
36	1930	M	33	Des	32	6.8	B	50	8
37	2160	F	34	Des + apn + cyan	47	3.7	B	28	4
38	2450	M	36	Des	41	1.0	A	20	—
39	3860	F	39	Other	23	11.2	C	50	5
40	2220	M	35	Des	40	13.8	C	80	7
41	1980	M	34	Des	39	5.5	B	60	9

apn = apnea; cyan = cyanoses; des = desaturation; RI = reflux index; SI = symptom index.

nine patients were excluded (5 presented neurological abnormalities, 2 were cardiopathic, and 2 presented a metabolic disorder). Therefore, 41 patients were included in the study. All of them had pathological cardiorespiratory monitoring. Thirty-three infants (80%) had a pathological pH-metry. Among them, 22 were included in group B, and 11 in group C.

All patients with GERD were pharmacologically treated until normalization of the monitoring and resolution of signs and symptoms were achieved. Subsequently, at follow-up no further clinical problem was recorded and no further ALTE episode was registered. Cardiorespiratory evaluations were performed monthly, at a mean time of 35 ± 5 days. A normalization of the tracks was recorded after a mean of 0.9 evaluations (1 month) for group A, six evaluations (7 months) for group B, and eight evaluations (9.5 months) for group C. A statistically significant difference was found in the time of normalization between different groups. In particular, a significant difference was noticed for both groups B and C when compared to group A ($p < 0.001$) as well as between groups B and C ($p < 0.05$). Linear regression analysis is shown in Figure 2.

Considering gestational age, six patients were born prior to the 30th week (mean 28 ± 1.2). All these patients presented a pathological pH-metry, and in four out of six patients (80%) GERD was considered severe. However, in
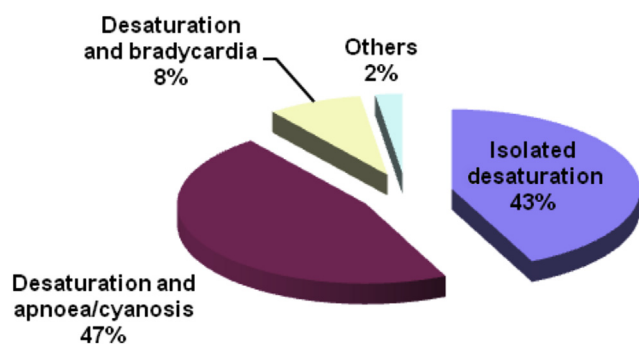
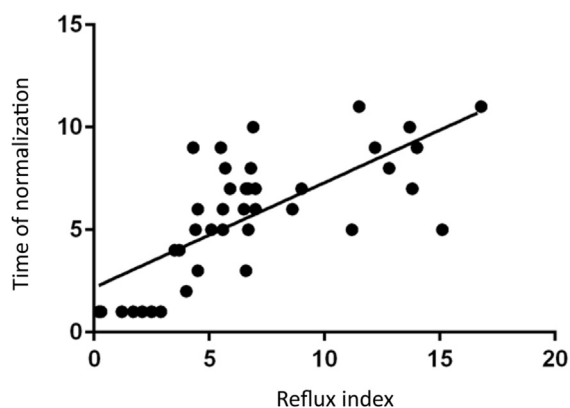**Figure 1** Apparent life-threatening event (ALTE): clinical manifestations.

Figure 2 Linear regression.

statistical analysis gestational age was not related to the prevalence of GERD ($p = NS$).

Eight patients were VLBW (mean weight, 1330 ± 112 g), six of whom presented GERD, which was severe in five patients. None of the patients was extremely low birth weight (<1000 g). Birth weight was not related to the prevalence of GERD. However, when considering only patients with GERD, birth weight was related to the severity of the disease ($p = 0.009$). No significant difference was recorded according to sex.

4. Discussion

ALTEs have been reported to occur in 0.5—10 children per 1000 live births.[11] There is significant evidence implicating GERD as one potential risk factor for ALTE, with a prevalence of about 31%.[12,13] There are two possible mechanisms by which GERD is thought to cause ALTE. The first one is a chemoreflex in the larynx triggered by the presence of refluxed gastric fluid.[14] The second one is the stimulation of the distal esophagus by the refluxed gastric fluids.[15]

Desaturation with apnea and cyanosis are the most common manifestations of ALTE (84%). Previously reported estimates of the prevalence of GERD in the general pediatric population varied from approximately 2% to 25% depending on the evaluated symptoms.[16] The prevalence of GERD in children who have symptoms suggestive of an ALTE was 42% in a previous study,[17] rising to 80% in our study.

These data may be attributed to the sensibilization of the problem from the first days of life in the neonatal intensive care unit and pediatric department, with careful monitoring and selection of patients. In fact, the treatment of reflux, when present, allows a rapid remission of symptoms and normalization of cardiorespiratory monitoring.

Birth weight seems to play a major role on GERD and its severity. No significant difference was recorded according to gestational age and sex. However, larger series may show different patterns of reflux in patients with different gestational ages at birth, thus leading to the definition of different reference ranges for RI according to birth age.

No other studies described the natural history of the correlation between GERD and ALTE.

On the basis of the reported results, it seems that the severity of GERD in terms of acid refluxes significantly influences the time of normalization of the cardiorespiratory monitoring. Furthermore, from the reported data, the time of remission seems to be strictly related to the severity of GERD: the worse the reflux, the longer the time of normalization of the cardiorespiratory tracks. In support of these considerations Valusek et al[4] suggested performing a fundoplication in children with GERD associated with repeated ALTE.

As a consequence, GERD always needs to be ruled out in the presence of episodes of ALTE in infants without other predisposing factors. As reported by many authors, pH monitoring is the most useful test for GERD, as it can be used over long periods and offers quantitative data.[18] Furthermore, it also allows prolonged monitoring with other physiological recordings in order to detect associated cardiorespiratory events in "at risk" infants.[19] Nevertheless, several technical limitations remain, related to pH probe monitoring and its efficacy in detecting the relationship between GERD and apnea. In particular, many refluxes may be undetected by the pH probe because of the frequent feedings of the infants, determining a prolonged elevation of gastric pH. In addition, nonacid reflux and rerefluxes that occur while the esophageal pH is still acidic may not be detected. The intraluminal impedance technique could offer more precise information about either weakly acidic or weakly alkaline episodes of reflux and also rerefluxes.[6,20] However, this complex technique still needs validated data concerning normal and pathological scores, especially in infants.[21,22] Although the measurement of multiple intraluminal impedance via the esophageal catheter in addition to esophageal pH has enhanced our understanding of GERD, it did not demonstrate a causal relationship between apnea and GERD. Therefore, we preferred to adopt only 24-hour pH-metry.[23]

5. Conclusion

GERD seems to play a crucial role in the etiopathogenesis and natural history of ALTE. The severity of GERD influences the time of normalization of cardiorespiratory monitoring, and antireflux therapy is helpful in preventing new episodes of ALTE. Because of its role, we strongly recommend investigating GERD in infants with ALTE in order to prevent further dangerous episodes.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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