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Factors associated with infant death after apparent life-threatening event (ALTE)

Mariana T. N. Romaneli,[1] Andréa M. A. Fraga,[2] André M. Morcillo,[3] Antonia T. Tresoldi,[3] Emílio C. E. Baracat[3]

Abstract

Objective: To detect factors associated with greater risk of death in infants after an apparent life-threatening event (ALTE).

Methods: This cross-sectional, retrospective, descriptive and analytic study evaluated infants younger than 12 months who had a sudden event of cyanosis, pallor, hypotonia or apnea and were seen in the emergency department of a tertiary university hospital. Forward stepwise logistic regression (Wald) was used to calculate and adjust odds ratios to evaluate associations.

Results: Mean age of the 145 patients included in the study was 105 days (median = 65 days). Eleven (7.6%) died, and their mean age was 189 days (median = 218 days). Mean age of survivors was 98 days (median = 62 days) (p = 0.003). Activity before the event, prematurity and number of events were not associated with death. A significant association was found with pallor. Of the 11 infants, 3 had spontaneous resolution of ALTE, whereas 8 patients [27.6%; p < 0.001; OR = 14.3 (95%CI 3.51-58.3)] did not. The associations with respiratory or cardiovascular disease were also significant. In multivariate analysis, immediate spontaneous resolution [p = 0.015; OR = 6.06 (95%CI 1.02-35.94)] and diagnosis of cardiovascular disease [p = 0.047; OR = 164.27 (95%CI 7.34-3.673.78)] remained statistically significant.

Conclusion: Infants who experienced an ALTE had a higher risk of subsequent death when their age was greater than 6 months and the event had a long duration, particularly when ALTE was associated with cardiovascular disease.

J Pediatr (Rio J). 2010;86(6):515-519: ALTE, apparent-life threatening event, death risk, infants.

Introduction

An apparent life-threatening event (ALTE) is defined as an alarming event characterized by a combination of central or obstructive apnea, change of skin color (pallor or cyanosis), change in muscle tone (hypotonia), choking or gagging.[1] It occurs without any evident cause in apparently healthy infants; although not infrequent, its progression is usually benign. However, the risk of subsequent death should be taken into consideration.[2-6]

Infants with ALTE are often brought to the pediatric emergency department only after full recovery, which may complicate the pediatrician's clinical reasoning to establish initial management. Such difficulty is primarily assigned to

1. Pediatrician. Department of Pediatrics, School of Medical Sciences (FCM), Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil.
2. Emergency pediatrician. MSc, Child and Adolescent Health, FCM, UNICAMP, Campinas, Brazil.
3. Associate Professor, Department of Pediatrics, FCM, UNICAMP, Campinas, Brazil.

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the event's specificity: it may affect healthy infants and have no pathological meaning, but it may also be the first sign of several diseases of variable levels of severity.[3,5,7-11,13-19]

In rare cases, infants with ALTE may have recurrent signs and symptoms and a progressively more severe clinical presentation than that of the initial event, and some may even require cardiopulmonary resuscitation. In such cases, they must be hospitalized for close observation, monitoring and a thorough workup.[2,6,9,12,16,19,20]

The management of infants with ALTE is difficult, and outcomes are unpredictable. This study evaluated factors associated with greater risk of death after ALTE.

Methods

This retrospective cross-sectional study described and analyzed data about 145 infants younger than 12 months who had a sudden event of cyanosis, pallor, hypotonia or apnea and were seen in the emergency department of Hospital de Clínicas of the Universidade Estadual de Campinas (HC-UNICAMP), a reference tertiary university hospital in a region with 6 million inhabitants. About 100 children are brought by parents or referred to its pediatric emergency department every day. The hospital has 48 beds in its pediatric ward and 10 beds in the pediatric intensive care unit (ICU).

Choking without cyanosis or febrile seizures, history of arrhythmias, cyanotic congenital heart disease, chronic lung disease, tracheotomy, epilepsy and chronic encephalopathy were exclusion criteria. Infants were also excluded if they had cardiopulmonary arrest on arrival and did not respond to resuscitation, in which case they were classified as victims of infant sudden death syndrome.[21] Therefore, only infants that responded to resuscitation and remained alive for at least 12 hours after ALTE were included in the study.

Data were collected from patient charts, and, for the patients that were seen more than once due to ALTE, only the event that justified hospitalization was recorded. Data were analyzed using the Statistical Package for the Social Sciences 16.0 (SPSS). The Mann-Whitney test was used for the age comparisons. To evaluate the association of the outcome variable (death) with the independent variables, logistic regression was used to calculate and adjust odds ratio. Variables that were significant in bivariate analysis were included in the unconditional multivariate logistic model. The level of significance was set at 5%. This study was approved by the Ethics in Research Committee of the School of Medical Sciences of UNICAMP (358/2009).

The Power Analysis and Interval Estimation tool of the software Statistica 5.5 (StatSoft, USA) calculated that 133 cases were necessary at an 80% power for a 3% incidence of death after ALTE (0 to 7.4% in the literature reviewed).[2,5,22-24]

Results

From April 2007 to September 2009, 175 patients met inclusion criteria, but 30 were excluded because they were discharged directly from the emergency department before 12 hours and their progression, therefore, was unknown.

In the sample of 145 patients, 51.7% were male and mean age was 105 days (median = 65 days). The activities before ALTE were: rest (49%), coughing (29.7%) and feeding (15.9%). The analysis of event that brought the patient to the hospital showed that cyanosis was the most frequent (84.8%), followed by hypotonia (37.2%), apnea (23.4%) and skin pallor (20.7%).

Most patients (55.9%) had only one ALTE: 11% had two, and 33.1% had three or more. Estimated duration was less than 1 minute in 45.5% and up to 5 minutes in 24.1% of the cases. The interval between event and patient arrival at the hospital was shorter than 60 minutes in 44.1% of the cases.

Initial examination revealed no physical signs or symptoms in 40.5% of the patients, tachypnea in 51%, hypoactivity in 36.6%, cyanosis in 25.5%, hypotonia in 22.1%, whizzing in 19.3%, cardiopulmonary arrest in 4.1%, apnea in 4.8%, and coma in 0.7%. Spontaneous recovery from the event was reported by parent or guardian in 51.7% of the cases; in 20%, there were no changes in condition regardless of maneuvers made by caregiver; 41.4% of the patients were kept under observation in the pediatric emergency department; 30.3% were admitted to the pediatric ICU; 20.7% were hospitalized in the pediatric ward; 6.2% were transferred to the neonatal ICU; and 1.4% were transferred to other hospitals in the region, all after a diagnosis was made.

Diagnoses associated with ALTE were made in 64.8% of the cases, and were more frequently associated with the respiratory tract diseases (38.6%). Other diagnoses were made (Table 1), such as acute diseases and comorbidities that had not been diagnosed before.

Of the 145 patients, 11 (7.6%) died during hospitalization. Their mean age was 189 days (median = 218 days); mean age of the patients that survived was 98 days (median = 62 days) ($p = 0.003$). Statistica analyses were made to evaluate the association between data collected and death.

Activity before the event and prematurity were not associated with death. The event description according to observer revealed that only pallor was significantly associated with death (Table 2).

The number of ALTE and the time interval until arrival at the hospital were not associated with subsequent death. Of the 11 infants that died, 3 recovered spontaneously, whereas 8 [27.6%; $p < 0.001$; OR = 14.3 (95%CI 3.51-58.3)] did not. Initial physical examination findings and their associations with death are shown in Table 3.

Table 1 - Diagnosis made for patients that had apparent life-threatening events and were seen in the pediatric department of the Hospital de Clínicas of Universidade Estadual de Campinas from April 2007 to September 2009

Diagnosis	N	%
Unknown	51	35.2
Acute viral bronchiolitis	31	21.4
Bacterial pneumonia	12	8.3
Pertussis-like cough	9	6.2
Urinary tract infection	7	4.8
Reaction to tetravalent vaccine	4	2.8
Gastroesophageal reflux disease	3	2.1
Viral myocarditis and cardiogenic shock	3	2.1
Meningoencephalitis	3	2.1
Acute viral gastroenteritis	2	1.4
Massive aspiration	2	1.4
Aortic arch malformation	2	1.4
Sepsis	2	1.4
Influenza A (H1N1)	2	1.4
Non-traumatic hemorrhage of central nervous system	2	1.4
Seizure due to central nervous system malformation	2	1.4
Congenital hypothyroidism	1	0.7
Abuse	1	0.7
Neonatal myasthenia gravis	1	0.7
Supraventricular tachycardia	1	0.7
Coma of unknown etiology	1	0.7
Refractory shock	1	0.7
Hyperbilirubinemia	1	0.7
Hypoglycemia	1	0.7
Total	145	100

Respiratory and cardiovascular diseases were significantly associated with greater risk of death. All significant parameters were included in multivariate analysis using a forward stepwise method (Wald), and results revealed a statistically significant association only with no spontaneous recovery [p = 0.015; OR = 6.06 (95%CI 1.02-35.94)] and a final diagnosis of cardiovascular disease [p = 0.047; OR = 164.27 (95%CI 7.34-3,673.78)] (Table 4).

Discussion

In this series, no significant association was found between ALTE and prematurity, a risk factor reported by several authors.[6,8,13,14,16] Also, gastroesophageal reflux, whose correlation with ALTE incidence ranges from 18 to 40% in most studies, had a low frequency in our series.[2,3,5,7,10,11,19] However, as reported by other authors, the most frequent causes of ALTE in this study were associated with respiratory diseases.[14,15]

This study showed that careful examination of infants with ALTE led to the diagnosis of the associated disease in 64.8% of the cases, a higher rate than those reported in most studies (about 40 to 55%),[3,6,12,13] but below those found in two prospective studies (77 to 83%).[2,10] The rate found in our study may be overestimated due to the exclusion of 30 infants that did not stay under observation in the pediatric emergency department and were excluded from the analysis for that reason.

Great age variability among patients with ALTE has been found, particularly because these events may be associated with several diseases. According to several studies, mean age ranges from 7 to 19 weeks,[3,4,10,13,17,25] whereas median age is 7 to 8 weeks.[2,6] Mean and median ages in our study were similar to those found in previous reports. Similarities were also found for mortality rates, which range from 0 to 7.4%.[2,4,5,22-24] However, a significant difference in the age of infants that died subsequently and those that survived was found in our study, but not in the literature reviewed.

Most hospitals admit patients based on their history and initial physical examination, and this is still the routine in our hospital. This may explain the difference in the literature about which infants should be hospitalized for

further examination. According to Davies & Grupta[2], as well as De Piero et al.,[25] age below two months is a risk factor for serious conditions, and these patients should remain under observation. Claudius & Keems,[16] however, classified infants older than 30 days who had only one event as low risk, and recommend discharge directly from the pediatric emergency department. In the study conducted by Al-Kindy et al.,[14] the following were found to be risk factors for desaturation and apnea: lower respiratory tract infection, prematurity and post-conception age < 43 weeks. Those authors suggested that infants with such characteristics should be monitored for at least 24 hours.[14]

Table 2 - Characteristics of apparent life-threatening events in the 11 infants that died according to information provided by observers, and their correlation with death

	Death					
Complaint	**n**	**%**	**Total**	**p**	**OR***	**95%CI**
Cyanosis	9	7.3	123	0.772	0.79	0.15-3.92
Pallor	5	16.7	30	0.045	3.63	1.02-12.85
Hypotonia	4	7.4	54	0.950	0.96	0.26-3.44
Apnea	2	5.9	34	0.669	0.70	0.14-3.44

95%CI = 95% confidence interval; OR = odds ratio; p = Wald test.
* Non-adjusted OR.

Table 3 - Initial physical examination parameters that were significantly associated with infant death after an apparent life-threatening event

	Death					
Physical examination	**n**	**%**	**Total**	**p**	**OR***	**95%CI**
CPA	2	33.3	6	0.033	7.21	1.16-44.86
Cyanosis	7	18.9	37	0.006	6.06	1.66-22.12
Hypotonia	8	25.0	32	< 0.001	12.21	3.01-49.46
Hypoactivity	10	18.9	53	0.004	21.15	2.62-170.60
Shock	6	42.9	14	< 0.001	18.89	4.72-75.52
Apnea	2	28.6	7	0.045	25.59	1.96-333.54

95%CI = 95% confidence interval; CPA = cardiopulmonary arrest; OR = odds ratio; p = Wald test.
* Non-adjusted OR.

Table 4 - Multivariate analysis of statistically significant parameters in the history of apparent life-threatening event considering initial physical examination and diagnosis

	Death					
	n	**%**	**Total**	**p**	**OR***	**95%CI**
Long event duration	8	27.6	29	0.047	6.06	1.02-35.94
Cardiovascular event	5	71.4	7	0.015	164.27	7.34-3,673.78

95%CI = 95% confidence interval; OR = odds ratio; p = Wald test.
* Adjusted OR.

No studies have evaluated the association of ALTE with subsequent death risk factors. Therefore, this study provides important information to be added to findings reported by other studies. It also suggests that infants with a prolonged ALTE and age 6 months or older form a group with a significant death risk, and should be hospitalized for a thorough workup. A higher frequency of diagnoses associated with ALTE in older infants has already been described by Etxaniz et al.[13] in a prospective study that found a greater prevalence of diseases associated with ALTE in infants older than 13 weeks.

A final diagnosis of cardiovascular disease, found to be a significant risk factor for subsequent death in multivariate analyses, is often made after hospitalization and examination of each infant and, obviously, cannot be used to guide management during the first evaluation of the patient in the emergency room.

This study has limitations that are inherent to retrospective series. Part of the sample (30 patients) was lost to analysis because of the unknown progression of infants with ALTE discharged directly from the pediatric emergency room in less than 12 hours after the event. Moreover, this study was conducted in a reference tertiary hospital, which may have affected the severity of final diagnoses and, consequently, death rates. However, findings suggest that potentially lethal diseases may be associated with ALTE.

Infants with ALTE had a higher risk of death when older than 6 months and there was no spontaneous resolution, particularly when the event occurred as the first sign of a cardiovascular disease.

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Correspondence:
Mariana Tresoldi das Neves Romaneli
Rua José Paulino, 1875/43-A – Centro
CEP 13023-102 – Campinas, SP – Brazil
Tel.: +55 (19) 3521.7322
Fax: +55 (19) 3521.7322
E-mail: matreneves@yahoo.com.br