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ORIGINAL ARTICLE

Independent risk factors for recurrence of apparent life-threatening events in infants

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Abstract The risk factors for recurrent apparent life-threatening event (ALTE) are unclear although the risk of recurrent ALTE is an important consideration for the management of ALTE patients. This study aimed to identify the risk factors for recurrent ALTE. We conducted a secondary analysis of the data from a single center retrospective cohort study in Japan conducted from March 2002 to January 2012, which included children diagnosed with ALTE at a pediatric emergency department (ED) in Tokyo. Among 112 ALTE patients, 18 (16%) had recurrences and 94 (84%) did not. Symptoms of respiratory tract infection (RTI) were more frequent in the recurrent group than in the non-recurrent group (44 *vs*. 14% $p = 0.0055$), and the proportion of patients triaged as level 1 was larger in the recurrent group than in the non-recurrent group (31 vs. 7%, $p = 0.0312$). Pallor was observed more frequently in the recurrent group than in the non-recurrent group (100 vs. 76%, $p = 0.0216$). Multivariate analysis demonstrated that the independent risk factors of recurrent ALTE were respiratory tract infection symptoms (OR, 5.02; 95% CI, 1.48–16.98).

Conclusion: ALTE patients who had RTI symptoms at the ED visit for first ALTE should be admitted for close observation of potential recurrences.

What is Known:
- *Approximately 10% of ALTE patients experienced recurrence of ALTE episodes.*
- *The risk of recurrent ALTE is one of the major consideration for the management of ALTE patients at the ED because these patients have higher rates of serious underlying diseases which require interventions.*

What is New:
- *Respiratory infection symptoms at ED presentation can be independent risk factors for recurrent ALTE.*

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Keywords Infantile apparent life-threatening event · Recurrence · Risk factors

Abbreviations

ALTE	Apparent life-threatening event
BRUE	Brief resolved unexplained event
ED	Emergency department
PICU	Pediatric intensive care unit
RTI	Respiratory tract infection

Introduction

An apparent life-threatening event (ALTE) was defined as "an episode that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging" at a consensus development conference convened by the National Institutes of Health in 1986 [1]. In May 2016, the American Academy of Pediatrics (AAP) published a new practice guideline for ALTE [13]. The guideline recommended the replacement of the term ALTE with "brief resolved unexplained event (BRUE)" because most of the ALTE patients had favorable outcomes in spite of its "life-threatening" nature. However, there are differences between the core concepts of managing ALTE and BRUE, and the clinical definition of BURE has yet to be widely accepted [13].

In recent years, the etiology and pathophysiology of ALTE are becoming established. Evidence has shown that most of the patients with ALTE had good outcome [4]. Therefore, researchers proposed that "low risk" ALTE patients who visited the emergency department (ED) could be managed without hospitalization [8]. For clinicians, the risk of recurrent ALTE is one of the major consideration for the management of ALTE patients at the ED because these patients have higher rates of serious underlying diseases which require interventions [10]. Several studies have shown that 10% of ALTE patients experienced recurrence of ALTE episodes [4, 7, 12], and one study suggested that patients with recurrent ALTE should be admitted for close observation and further investigation for underlying disease [7].

To date, the risk factors for recurrent ALTE have not been fully investigated. The aim of this study was to identify these risk factors.

Subjects and methods

Design

This was a secondary analysis of data from a single center retrospective cohort study in Japan conducted from March 2002 to January 2012 and published in Japanese [14]. We included children diagnosed with ALTE at our ED during the study period but excluded children older than 1 year. The definition of ALTE was based on the National Institutes of Health Consensus Development Conference Statement [1]. We defined recurrent ALTE here as an episode sharing the same clinical features as the first episode of ALTE experienced by the patient. In particular, in-hospital recurrent ALTE was also defined as a clinical state that needed resuscitation to stabilize compromised respiratory and/or circulation, convulsions, and bradycardia due to hypoxia during hospitalization.

Chart review method

The chart review was conducted using a structured method [6]. We trained the designated abstractor (UR) in the abstraction method before data abstraction, constructing the abstraction form, and defining the variables through discussions with the investigators (UR, ON, and TM). After data abstraction was begun, we periodically held meetings (UR, ON and TM) to examine the abstracted patient data randomly.

Study setting

The National Center for Child Health and Development is a tertiary care pediatric and perinatal hospital in Tokyo, Japan. Each year, about 35,000 children visit the emergency department of the hospital. The hospital has 320 beds, including 40 neonatal intensive care unit beds and 20 pediatric intensive care unit (PICU) beds.

Data collection

Patients characteristics

We investigated the age, gender, birth history, underlying diseases, and symptoms of patients observed by their caregiver at the time of ALTE. Those symptoms were categorized into "pallor," "hypotonia," "breathing difficulties," "blue/cyanotic," "abnormal eye movement," "excessive mucus production," "red, hypertonic/overdistention/crying," and "vomiting and jerkin limbs," according to Semmekrot et al. [11]. The presence of respiratory tract infection (RTI) symptoms such as cough and nasal discharge was evaluated by physicians at the ED. The triage level of the patients, PICU admission, and definitive diagnosis of the patients at discharge were also investigated. For the determination of the patients' triage level, trained nurses triaged all the patients who visited the ED according to the Canadian Pediatric Triage and Acuity Scale (P-CTAS) [15]. In general, triage level 1 is assigned to patients who present with severely unstable vital signs and to those who require immediate interventions to be stabilized.

Recurrence of ALTE and prognosis

We reviewed the incidence of recurrent ALTE by reviewing patient charts for the 6 months after the first incident of ALTE. The prognosis of the patients was also studied. Patients were identified as alive without recurrent ALTE if they had follow-up outpatient visit in the 6 months after the first incident and if there was no record of recurrent ALTE. Patients who did not come to the hospital for a follow-up visit during that time were deemed as unknown outcome.

Eventually, we compared the characteristics of the patients who experienced recurrent ALTE with those who did not.

Analysis

Data were analyzed using JMP11 (SAS Institute Inc., Cary, NC). In univariate analysis, continuous variables were compared by the Mann-Whitney *U* test and categorical variables by the Fisher's exact test. The significance level was set at $p < 0.05$. Logistic regression was used to determine the independent risk factors for recurrent ALTE. We selected candidate variables for analysis based on a review of the literature. From among these, we then identified variables for logistic regression analysis by calculating Akaike's Information Criterion (AIC) by forward selection.

Results

Patient characteristics

A total of 112 patients diagnosed with ALTE were identified during the study period (Table 1). Fifty-five (49%) patients were male, and there were nine (8%) patients whose gestational age was less than 36 weeks. Sixteen (14%) patients had underlying disease and 62 (55%) patients were less than 2 months old at the time of ALTE. At the ED presentation, 21 (19%) patients had RTI symptoms. Eleven (10%) patients were triaged as level 1 because of extremely unstable vital signs due to respiratory failure (six patients), compromised cardiopulmonary state (three patients), disturbed consciousness (one patient), and hypothermia (one patient). Among 11 patients assigned to triage level 1, two patients had history of premature birth (gestational age < 36 weeks) and eight patients were younger than 2 months of age at presentation. Five patients were intubated due to respiratory failure but no patients needed cardiopulmonary resuscitation. RTI was definitively diagnosed in five patients, gastroesophageal reflux in two patients, epilepsy in one patient, choking in one patient, and hypothermia in one patient. The diagnosis was indeterminate in one patient. Of 102 (92%) hospitalized patients, 15 (13%) were admitted to the PICU. Among the 15 patients who were admitted to the PICU, two patients had history of premature birth and nine patients were younger than 2 months of age at presentation. Six patients were intubated due to respiratory failure but no patients needed cardiopulmonary resuscitation. RTI was definitively diagnosed in seven patients, idiopathic apnea in three patients, gastroesophageal reflux in one patient, and choking in one patient. The diagnosis was indeterminate in three patients.

Recurrence of ALTEs

Eighteen (16%) patients experienced recurrent ALTE (Fig. 1). Among them, 15 experienced recurrence during hospitalization and three did so after discharge following hospitalization. Among the 15 patients who had recurrent ALTE during hospitalization, we confirmed that ten patients were alive 6 months after the first ALTE incident. Four patients could not be followed up (unknown) and one patient died. The patient who expired was a previously healthy 1-month-old female. She was initially brought to the ED because her parents saw that she had apnea. On arrival, she presented repeated apnea during the examination in the ED and was intubated.

Table 1 Characteristics of patients with ALTE

	Total (n = 112)	Recurrent (n = 18)	Non-recurrent (n = 94)	P
PICU admission	15/112 (13)	11 (61)	4 (4)	<0.0001
RTI symptoms at ED presentation	21/112 (19)	8 (44)	13 (14)	0.0055
Level 1 triage	11/112 (10)	5 (31)	6 (7)	0.0132
Male	55/112 (49)	11 (61)	44 (47)	0.3105
Underlying disease	16/112 (14)	1 (6)	15 (16)	0.4615
Age <2 months at the incident	62/112 (55)	11 (61)	51 (54)	0.6173
Gestational age <36 weeks	9/111 (8)	2 (11)	7 (8)	0.6392

Values are numbers (%)

ALTE apparent life-threatening event, *PICU* pediatric intensice care unit, *RTI* respiratory tract infection, *ED* emergency department

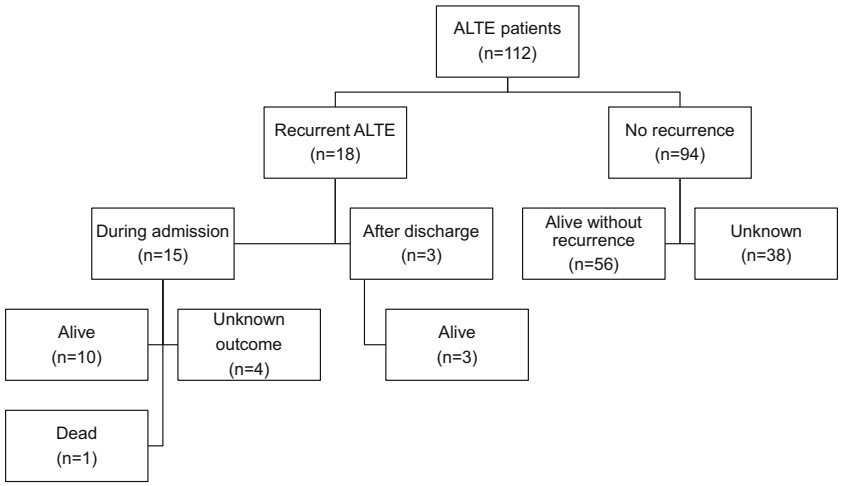

Fig. 1 Derivation of study cohort

Finally, she was admitted to the PICU and received intensive care for 2 weeks. The definitive diagnosis in her case was respiratory failure due to a viral respiratory tract infection. She was discharged without any symptoms after 1 month's hospitalization. However, a month thereafter, she was found in the morning apneic and pulseless by her parents who had been cosleeping with her and was brought to the ED in a state of cardiopulmonary arrest. She failed to respond to resuscitation and expired. Although autopsy was performed, the cause of death was not determined.

All three patients who had recurrent ALTE s after discharge were confirmed to be alive. Of the 94 patients without recurrence, 56 were confirmed to be alive 6 months after the first ALTE and 38 were unknown.

Gender, birth weight, gestational age, age, presence of underlying disease, and nutrition were similar between the patients with recurrent ALTE and the patients without. RTI symptoms were more frequent in the recurrent ALTE group (44 vs. 14%, $p = 0.0055$). The proportions of patients triaged as level 1 (31 vs. 7%, $p = 0.0132$) and of those who needed intensive care (61 vs. 4%, $p < 0.0001$) were larger in the recurrent ALTE group than those in the non-recurrent group (Table 1). As for the symptoms observed shortly after the episode, pallor was observed more frequently in the recurrent ALTE group than in the non-recurrent group (100 vs. 76%, $p = 0.0216$). The frequency of hypotonia was slightly higher in the recurrent ALTE group than in the non-recurrent group (61 vs. 39%, $p = 0.1191$), although the difference was not statistically significant (Table 2). There was no statistical difference in the prevalence of definitive diagnosis between the two groups (Table 3).

Multivariate analysis showed that RTI symptoms at ED presentation (odds ratio [OR], 5.02; 95% confidence interval [CI], 1.48–16.98) was an independent risk factor significantly associated with recurrent ALTE. Prolonged unstable vital signs (level 1 triage) were also likely to be a risk factor; although, the analysis did not show statistical significance (odds ratio [OR], 4.32; 95% confidence interval [CI], 0.97–18.47) (Table 4).

Table 2 Symptoms of the patients shortly after ALTE

	Recurrent ($n = 18$)	Non-recurrent ($n = 94$)	p
Pallor	18 (100)	71(76)	0.0216
Hypotonia	11 (61)	37 (39)	0.1191
Excessive mucus production	1 (6)	20 (21)	0.1870
Red	0 (0)	14 (15)	0.1204
Hypertonia	1 (6)	8 (9)	1.0000
Vomiting	1 (5)	6 (6)	1.0000
Jerkin limbs	1 (6)	3 (3)	0.5090

Values are numbers (%)

ALTE apparent life-threatening event

Table 3 Definitive diagnosis of the patients

	Recurrent ($n = 18$)	Non-recurrent ($n = 94$)	p
Breath-holding spell	3 (17)	4 (4)	0.0811
Respiratory tract infection	5 (28)	11 (11)	0.1322
Choking	0 (0)	12 (13)	0.2089
GER	3 (17)	27 (29)	0.3900
Apnea	3 (17)	11 (12)	0.6959
Epilepsy	0(0)	5(5)	1.0000

Values are numbers (%)

GER gastroesophageal reflux

Table 4 Adjusted risk of recurrent ALTE

Characteristics	Odds ratio	95% CI	*p*
RTI symptoms at ED presentation	5.02	1.48–16.98	0.0102
Level 1 triage	4.32	0.97–18.47	0.0546

ALTE apparent life-threatening event, *RTI* respiratory tract infection, *ED* emergency department

Discussion

To the best of our knowledge, this is the first study that investigated the risk factors for recurrent ALTE. We identified that RTI symptoms at ED presentation were an independent risk factor for recurrent ALTE.

The literature has highlighted that recurrent ALTE may indicate the underlying pathology of patients [2, 5, 9, 12]. A multicenter prospective study of ALTE developed a prediction model for the need of hospitalization and identified three variables [7]. They are "obvious need for admission," "significant medical history," and "the recurrence of ALTE within 24 hours". In the study, "obvious need for admission" was defined as requiring supplemental oxygen, intubation, ventilation, intravenous antibiotics for serious bacterial infections, antiepileptic drugs for status epilepticus, or if the patient was tested positive for respiratory syncytial virus or pertussis. Another retrospective study reported that the presence of upper respiratory tract infection symptoms was one of the predictors of extreme events in infants hospitalized for ALTE [3]. The findings of these studies corroborate with ours which showed that patients who had RTI symptoms and/or prolonged unstable vital signs at ED presentation were likely to experience recurrent ALTE.

As previous studies have suggested, recurrent ALTE was a significant predictive factor for hospitalization [7]. However, those studies did not indicate which patients were likely to experience recurrence. Our findings may be helpful for physicians to predict the risks for recurrent ALTE.

There are several limitations in this study. First, this was a retrospective study conducted in a single pediatric hospital in Japan. Thus, the generalizability of our findings is unclear. Second, the abstractor was not blinded to the study objective and patient assignment in the data collection process, thereby possibly causing a bias in the analysis [6]. Third, the follow-up duration for the study cohort was inadequate. Notably, the prognosis for nearly 40% of the patients was unknown. If those patients had recurrent ALTE beyond the follow-up period of this study, the results might have been different. Nonetheless, our hospital is the only one in western Tokyo area that has a pediatric ED and we routinely instruct ALTE patients to return to our ED in case of recurrences. Although we failed to follow up on a certain proportion of patients, it was unlikely that it had a major influence on our results.

In conclusion, this study illustrates that RTI symptoms and/or prolonged unstable vital signs at the first ALTE can be independent risk factors for recurrent ALTE. Patients with ALTE who had those symptoms should be admitted for close observation of potential recurrences.

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Authors' contributions RU: All facets of the study from study design to data collection and analysis and finally, completion of the manuscript. ON: Study concept development, design, data interpretation, and manuscript review. TM: data analysis and manuscript revision. HS and SN: Interpretation of the data and manuscript review. AI: Interpretation of the data and manuscript revision and editing. All authors read and approved the final manuscript.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethics Committee at the The National Center for Child Health and Development.

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