Apparent Life-Threatening Events: Patients' Health Status at 5 Years of Age

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ABSTRACT: **Background:** The long-term significance of apparent life-threatening events (ALTE) has not been thoroughly studied.
Objectives: To evaluate, at age 5 years, the health status of consecutive children diagnosed with ALTE in infancy.
Methods: Based on the diagnostic workup, patients were classified into two groups: a 'broad' evaluation group (at least one test/procedure related to each of the five main causes: infectious, metabolic, cardiopulmonary, gastroenterological, neurological), and a 'narrow' workup group whose evaluation did not cover all five domains. Health status around age 5 was obtained from hospital records, community clinics and parents/caregivers.
Results: We identified 132 children with ALTE. Choking (49.2%) was the most common description, followed by apnea (13.6%), suspected seizure (12.9%), cyanosis (12.1%), breath-holding spell (8.3%), and pallor (3.8%). A broad diagnostic workup was performed in 62.1% of the infants, and a narrow workup in 37.9%. At age 5 years, 56.8% of the children were healthy; 27.3% reported chronic conditions unrelated to ALTE. Twenty-one children (15.9%) had unrelated neurodevelopmental conditions, mostly attention deficit disorder. One of the 132 ALTE patients relapsed and was eventually diagnosed with epilepsy.
Conclusions: A single episode of ALTE in infancy was neither predictive of nor associated with chronic systemic or neurological disease at age 5 years.

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KEY WORDS: apparent life-threatening event (ALTE), long-term outcome, neurodevelopmental conditions

An apparent life-threatening event (ALTE) is a major reason for referral to the emergency department and for hospital admission. Although its exact incidence is not well defined due to the heterogeneous nature of the events, it has been estimated that 0.6–0.8% of all pediatric emergency room visits and 2.27% of all pediatric admissions are due to ALTE [1]. ALTE was defined by the National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring as "an episode that is frightening to the observer and 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" [2]. ALTE is indeed a frightening event for parents and caregivers. Since the infant usually appears healthy by the time of clinical evaluation, clinical characterization of the event by the physician may be quite difficult [3].

Historically, the significance of ALTE lay in the belief that it precedes sudden infant death syndrome (SIDS) as ALTE was often considered an aborted SIDS episode, hence its former name "near SIDS." Evidence in the last decade has clearly shown that ALTE and SIDS are unrelated, and patients who experience ALTE are not at risk for SIDS later on [4].

Nevertheless, infants admitted for ALTE frequently undergo a series of diagnostic procedures to both rule out an immediate health threat as well as detect a risk for future ALTE events and SIDS [3,5,6]. Evidence suggests that the yield for broad diagnostic tests is generally low unless these procedures are steered by specific history details or physical findings [7]. Since ALTE rarely recurs, many patients are managed conservatively [8] and discharged from the emergency room (ER) [9].

Most reports on ALTE evaluation focus on establishing the cause of the event and the short-term outcome. Since, to the best of our knowledge, an assessment at a later age of children who underwent ALTE in infancy has not been performed, we sought to determine the health status of ALTE patients at age 5 years, paying particular attention to whether ALTE may have been a predictor or was the first manifestation of a chronic illness of any kind.

PATIENTS AND METHODS

This study was performed with the approval of the Internal Review Board of Meir Medical Center. Medical records of all patients evaluated for ALTE at Meir Medical Center between 2000 and 2005 were reviewed. Emergency room guidelines during the study period required hospital admission for all ALTE patients. The diagnosis of ALTE appeared in the discharge summary of these infants, although other terms – such as apnea, choking, pallor – were often listed as the event lead-

ing to hospitalization. The information gathered on ALTE patients related to two periods in their clinical history: (i) the initial hospital admission, and (ii) age 5 years.

Data obtained from admission included: demographic information such as age, gender, ethnicity (Jewish, Arab, other), previous medical history, relevant family history, description of the ALTE event, clinical status and physical findings, diagnostic workup, and etiology, if established, of the ALTE event. Based on the extent of the diagnostic workup, patients were classified into two groups: those who underwent a broad evaluation (at least one test/procedure related to each of the five main etiologic groups: infectious, metabolic, cardiopulmonary, gastroenterological, neurological), and those with a narrow workup who underwent diagnostic procedures that did not cover all five etiologic domains.

Information on the health status around age 5 was obtained from several sources. Since Meir Medical Center is the only referral center in the area, many records were available from ambulatory services/admission records as these patients were followed by different specialists according to the symptomatology on admission or the diagnostic workup during their hospital stay. Further data were obtained from primary care physicians in the community who followed the patients. In a few cases, information was gathered from patients' parents or caretakers by telephone. The information sought on the patient's status included: recurrence of the ALTE event, the occurrence of SIDS, whether the ALTE event preceded the development of a serious illness or a chronic condition and, if it indeed occurred, was the disease still active by age 5. Data on the neurodevelopmental history and status of the patient were gathered from clinical charts, and/or by asking parents, caregivers, and in some cases primary care physicians, the following questions:

- Did the child exhibit any type of developmental delay and if so, which area of neurodevelopment was affected?
- Was follow-up/treatment at a child development institute needed?
- Has the child needed any type of special education?
- Was the diagnosis of ADHD considered in this child?

Our aim was to assess the 5 year outcome of infants who were considered healthy when ALTE occurred. We believe this population would be representative of 'true ALTE', compared to infants with acute life-threatening conditions who may be at risk for acute events (such as seizures or respiratory distress). Therefore, we excluded from the study infants with a history of prematurity, as well as term infants with hypoxic-ischemic encephalopathy or other major perinatal complications, babies born following a high risk pregnancy or with a maternal history of intrauterine infection or chronic illness. Regarding infant physical abuse, fortunately still rare in Israel, these babies were not included as their discharge summary diagnoses did not include the term ALTE

RESULTS

A total of 132 cases were identified (53% females). The age at presentation ranged between 5 days and 11 months (75% before 3 months of age); the mean age was 9.6 ± 9.4. All patients were admitted to the hospital. We did not identify any case of parents or caretakers refusing admission.

Choking was the most common witness description of the ALTE event, occurring in 49.2% of cases, followed by apnea (13.6%), suspected seizure (12.9%), cyanosis (12.1%), breath-holding spell (BHS) (8.3%), and pallor (3.8%) [Figure 1]. Gender distribution was similar for the most common presentations, but breath-holding spells showed a marked male predominance, and all five cases of pallor occurred in girls. We did not identify any case of non-accidental trauma among the 132 babies admitted with ALTE.

A broad diagnostic workup was performed in 82 cases (62.1%), while a narrow workup was obtained in 37.9% [Figure 2]. Regarding the presumed etiologies leading to the ALTE event, the diagnostic workup (irrespective of being broad or narrow) was normal in 46 of the 132 cases (32%). Gastroesophageal

Figure 1. Witness description of ALTE event, in percentages

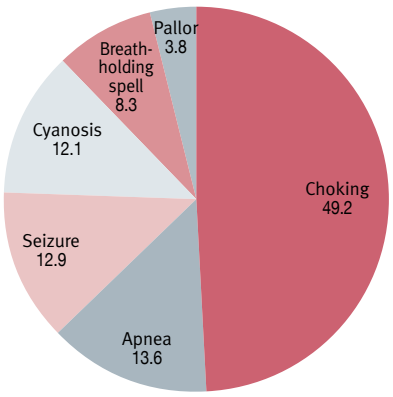
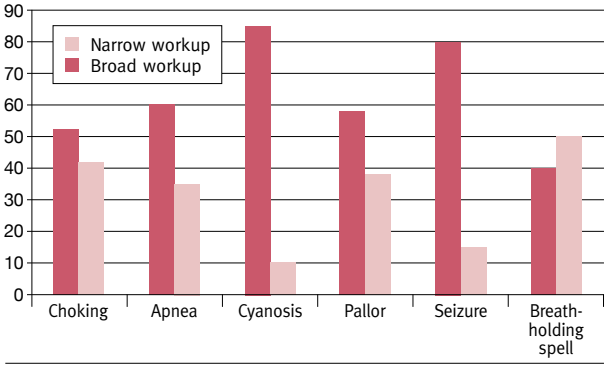


Figure 2. Type of diagnostic workup in relation to clinical description of ALTE event



reflux (GER)/overfeeding was the most common cause in the remaining cases (30%). For this final diagnosis, a broad diagnostic approach was performed in most cases [Table 1].

Data on the health status at age 5 years were available for 132 children. Most patients (56.8%) were healthy; 27.3% were reported as having chronic conditions deemed not related to the ALTE event, such as dermatitis, obesity, orthopedic complaints, and asthma (developing at least 1 year after ALTE). Five infants had been diagnosed with mild cardiac defects (four with patent foramen ovale, one with atrial septal defect), and all were healthy at age 5 years. Regarding the possibility of a missed diagnosis of physical abuse at the time of admission, the 5 year follow-up did not uncover any case among the 132 ALTE patients.

Twenty-one children (15.9%) had been diagnosed with neurodevelopmental conditions, such as attention deficit disorder (15 cases), epilepsy (2), and 1 case each of hydrocephalus, neurofibromatosis, selective mutism, and migraine [Table 2]. Analysis of the 15 ADHD cases did not reveal a particular type of ALTE manifestation, and the etiology for this specific subgroup was distributed similarly to that of the remaining ALTE cases. The child with hydrocephalus presented at 1 month of age with "choking-type" ALTE secondary to GER. Non-communicating hydrocephalus was diagnosed at the age of 3 years after normal development. Regarding epilepsy, one girl with ALTE at age 5 days (cyanosis) who developed normally was diagnosed with benign occipital epilepsy at 5 years; therefore, the ALTE event was probably not related to further epilepsy. However, the second baby, a 3 month old girl admitted for suspected seizures (clonic, alternating in location), continued to have seizures during the months that followed ALTE and was found to have brain cortical dysplasia.

Finally, analysis of the ALTE type by gender shows that for the most prevalent ALTE types, i.e., choking, apnea, cyanosis and suspected seizure, the distribution of events was similar for both genders. Nevertheless, regarding less common presentations, most of the 11 BHS patients were boys, whereas all 5 pallor patients were girls.

Table 1. Presumed etiologies for ALTE following admission

	Diagnosed (%)	Type of workup
Normal	46 (34.8)	Broad 33 Narrow 13
GER/overfeeding	33 (25)	Broad 21 Narrow 12
URTI/RSV	18 (13.7)	Broad 4 Narrow 14
Swallowing difficulty/ vomiting	15 (11.4)	Broad 10 Narrow 5
Breath-holding spell	10 (7.6)	Broad 5 Narrow 5
Other	10 (7.5)	Broad 9

GER = gastroesophageal reflux, URTI = upper respiratory tract infection, RSV = respiratory syncytial virus

Table 2. Neurodevelopmental diagnosis at age 5 years in 21 of 132 cases

Health status	No. of patients	%
Healthy	75	56.8
Conditions unrelated to ALTE	36	27.3
Neurodevelopmental diagnoses	21	15.9
ADHD	15	
Epilepsy	2	
Hydrocephalus	1	
Migraine	1	
Neurofibromatosis	1	
Selective mutism	1	

ADHD = attention deficit hyperactivity disorder

DISCUSSION

Until recently, ALTE was feared to be predictive of sudden infant death syndrome (SIDS). Nonetheless, its possible role as the initial manifestation of a serious or chronic disease is still a matter of controversy. Accumulating evidence suggests that SIDS is not preceded by ALTE and ALTE does not predict SIDS [7,18,10]. In addition, the decline in incidence of SIDS following the recommendation that young infants sleep in the supine/sideways position was not accompanied by a reduction of ALTE cases [11]. Despite this, there is still wide variation in the diagnostic approach to these infants: a recent survey of 255 emergency medicine physicians in Michigan showed that most would obtain laboratory tests (complete blood count, serum electrolytes, serum glucose, urine analysis). Moreover, most would consult various subspecialties for managing these children [12]. A retrospective review of diagnostic procedures among 243 infants with ALTE during the period 1996–1999 revealed that 3776 tests had been performed but only 5.9% helped determine the cause of the event. For patients with a contributory history/physical examination, the studies with the highest yield were blood counts, chemistries and cultures; cerebrospinal fluid analysis and cultures; metabolic screening; screening for respiratory pathogens; screening for GER; and chest radiograph, brain neuroimaging, skeletal survey, electroencephalogram (EEG), echocardiogram and pneumogram. Most importantly, for patients without a contributory history/physical examination, only screening for gastroesophageal reflux, urine analysis and culture, brain neuroimaging, chest radiograph, pneumogram, and white blood cell count were useful [7].

The possibility that ALTE may be the presenting symptom of a serious bacterial infection has also been studied. A 2007 study showed that in most cases, signs or symptoms of infection are evident at the initial evaluation following an ALTE episode. However, since in some cases with urinary tract infection or pneumonia, clinical signs of the disease may be absent during the first hours, ALTE may rarely be a manifestation of bacterial infection [13], particularly among very young infants

and premature babies [14]. Indeed, 2 infants in a series of 176 cases (all but one were admitted) died after being discharged and within 2 weeks of the ER evaluation. Diagnostic workup in the ER was negative in both cases. Pneumonia was listed as the cause of death by the coroner [15].

Our study was not designed to determine the yield of specific diagnostic procedures in uncovering the etiology of the ALTE episode, or to establish the extent of the diagnostic workup in these infants. Hence, data on specific causes of ALTE in our patients are not reported here. This study aimed at evaluating the impact of ALTE, if any, on the long-term health status of these infants in an attempt to verify our assumption that ALTE in infancy in an otherwise healthy baby is not predictive of chronic illness.

Since our medical center is the only major referral center in the region and all ALTE cases in Israel that occurred during the study period were admitted to our center for inpatient evaluation, our 132 cases are representative of the management and ultimate prognosis of ALTE in our district.

We found no cases of later SIDS among our ALTE patients, in concordance with the current literature. Moreover, no later mortality cases were detected. ALTE did not recur, except for the single case of a female infant whose ALTE episode was in fact her first epileptic seizure. In this case, all the attacks that followed the ALTE episode were obvious epileptic fits.

Regarding the diagnostic evaluation, about two-thirds of the infants belonged to the 'broad' group, particularly if the ALTE episode was described as cyanotic or a seizure. Pallor and apnea also showed a preference, albeit less marked, for a broad workup. Conversely, choking and BHS events were equally distributed between the 'broad' and the 'narrow' evaluation groups. Of note, the decision as to which diagnostic approach to take in each individual case was made by the attending physician in the ER. Furthermore, the fact that most infants underwent a broad diagnostic workup probably reflects the common assumption during the study period that ALTE could precede SIDS or was the presenting symptom of a serious condition. As noted, recent evidence demonstrates that a more judicial, symptom-directed approach is more effective in establishing the cause of the event.

According to a recent systematic review on the management of ALTE, there is still insufficient evidence to determine the clinical history or features predictive of further ALTE or of impending serious health condition. Moreover, no conclusions could be drawn regarding a universal, high yield diagnostic procedure. Nevertheless, routine screening tests for gastroesophageal reflux, meningitis, bacteremia and seizures show low yield in infants without historical risk factors or suggestive physical examination findings [16].

While the literature on the immediate cause of ALTE and the yield of the diagnostic workup is extensive, only a few studies have addressed the issue of long-term outcome. ALTE was shown to have a low predictive value for later childhood heart disease [10]. We did not detect any case of chronic cardiac disease at age 5 years among our 132 patients, although 5 infants had transient mild congenital cardiac defects that did not necessitate specific treatment and had resolved spontaneously by age 5. Otolaryngology causes were later recognized in only 0.6% of cases during a 5 year follow-up [17]. Complications of gastroesophageal reflux as the cause of ALTE are also rare [18].

In our study, ALTE was not the presenting symptom of infant abuse or of shaken baby syndrome. A single study addressed the risk for later mortality, an eventual diagnosis of infant abuse, and later severe neurological morbidity among 471 babies diagnosed with ALTE. Of all ALTE cases, 11% were later diagnosed with physical abuse and about 5% developed serious neurological conditions, mostly epilepsy [19].

Miloti and Einspeler [18] compared the neurological long-term prognosis in a small series of 14 ALTE cases with that in 12 controls. Patients were evaluated at a mean age of 14.4 years. All ALTE episodes had occurred before 9 weeks of age: four children showed minor neurological deficits (MND) – defined as "deficits resulting in an impairment that did not lead to a disabling condition," and one (who needed CPR during the ALTE episode) showed severe learning difficulties. Since MND, a term recently replaced by "Developmental Coordination Disorder (DCD)," is a common occurrence (20–35%) in children, the association between ALTE and MDN in Miloti's series may not be as strong as the authors suggest [20].

We did not perform a neurodevelopmental assessment at age 5 years in our patients since our study was based on clinical charts and parental reports. Nevertheless, the prevalence of significant neurodevelopmental issues, as reported by parents/caregivers, was low: 15 of the 132 children having signs and symptoms of ADHD. This apparent high incidence may be associated with the increased rate of ADHD diagnosis in Israel in recent years and is likely unrelated to the single ALTE episode in infancy [21]. Of the two infants who developed epilepsy, one exhibited true focal seizures that had initially been misdiagnosed as ALTE but the epileptic nature of her events was established shortly after the "ALTE" episode. In neither of the two epilepsy patients was apnea the manifestation of ALTE. Apnea may be the initial expression of partial epilepsy in infancy and can be initially diagnosed as ALTE, especially since interictal EEG may be normal in these cases [22]. Since ALTE rarely recurs, relapsing apneic spells in an otherwise healthy-looking infant should raise the possibility of epilepsy. As noted, neither of our two epilepsy infants presented with apnea.

In conclusion, in this series of 132 patients, a single episode of ALTE in infancy was neither predictive of nor associated with chronic systemic or neurological disease at age 5 years. No cases of later mortality or of SIDS occurred following the ALTE episode. These findings support the changing clinical approach to a first ALTE episode from a more inten-

sive (and costly) diagnostic workup to a more conservative symptom-directed workup, including clinical observation without laboratory procedures in healthy-looking infants following the ALTE event.

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