

Apparent life-threatening events and brief resolved unexplained events: management of children at a Swiss tertiary care center

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Summary

AIMS OF THE STUDY: Apparent life threatening events (ALTEs) are highly stressful situations for the caregiver and commonly result in presentation of the child to an emergency department. As the events are usually brief and resolve in a short period of time, the entity is now called a brief resolved unexplained event (BRUE). Updated recommendations have been published in recent years on the management of BRUE, including a risk stratification to identify those at lower risk for subsequent events or severe underlying disorders. The aim of this study was to describe the epidemiology of ALTE and BRUE at our hospital and detail clinical practice of management in this population in a tertiary care children's hospital in Switzerland.

METHODS: We retrospectively analysed all cases of children with an ALTE or BRUE admitted to the University Children's Hospital Basel between September 2009 and April 2018, identified using ICD-10GM coding. Electronic health records were used to extract data on diagnostic procedures, duration of admission and outcome. Infants with a lower-risk BRUE (defined as age >60 days and <1 year, born at ≥32 weeks gestational age and postconceptional age ≥45 weeks, first BRUE episode with a duration of <1 minute and no cardiopulmonary resuscitation by trained medical provider required) were compared with those with a higher-risk BRUE/ALTE (not fulfilling all the criteria for lower-risk BRUE).

RESULTS: A total of 65 patients with a median age of 42 days (interquartile range 20–67) were identified, of whom 15% were classified as having a lower-risk BRUE. A blood sample was analysed in 97% of patients, cranial ultrasound was performed in 63%, an electrocardiogram in 78% and polysomnography in 26%. The results remained normal in almost all patients and none had a further event recorded during admission. In one patient only QTc prolongation was detected as a potential serious underlying disease.

CONCLUSIONS: Our data show that admission for more than 24 hours and extensive investigations for infants admitted for an ALTE/BRUE rarely led to identification of specific underlying causes. According to current recommendations, 15% of the admitted patients could be categorised as having a lower-risk BRUE and therefore hospital admissions and investigations can safely be reduced. We propose an adaptation of the current Swiss recommendations for ALTE/BRUE to optimise clinical management of children presenting with a BRUE.

Introduction

Approximately 1% of all emergency department visits by children below one year of age are due to apparent life-threatening events (ALTEs) or brief resolved unexplained events (BRUEs) [1–3]. Reports on the incidence of ALTEs show a broad range from around 0.46/1000 to 10/1000 live births, with decreasing rates over recent years in developed countries [4–7]. An ALTE is defined by signs alarming to the observer, which include one or more of the following: dyspnoea, colour change, change in muscle tone with choking or gagging requiring stimulation [2]. Due to the difficulty in applying "ALTE" to clinical care and research, "BRUE" was introduced as a new term [8]. BRUE describes an event in children younger than one year of age that is "brief" defined as shorter than one minute duration and "resolved" as witnessed by the observer and furthermore involves ≥1 of the following: (1) cyanosis or pallor; (2) absent, decreased or irregular breathing; (3) marked

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ABBREVIATIONS

ALTE	apparent life-threatening event
BRUE	brief resolved unexplained event
ICD-10GM	International classification of diseases German modification
IQR	interquartile range
RSV	respiratory syncytial virus

change in tone (hyper- or hypotonia); and (4) altered level of responsiveness [9] (table 1).

Despite the self-limiting nature of the events, many families present to emergency departments and the challenge for the paediatrician is to identify infants with a severe underlying disorder requiring further diagnostic tests and treatment to prevent life-threatening events. Recommendations for the management of children presenting with an ALTE by the Swiss Society of Paediatrics were published in 2007 and include admission and cardiorespiratory monitoring for 48 to 72 hours [10]. In addition to this the recommendation suggested investigations if the reason for the event remains unclear, including a full blood count, analysis of respiratory viruses in a nasopharyngeal swab, electrocardiogram (ECG), ophthalmology review, polysomnography and an electroencephalogram (EEG). However, there is no recommendation as to the priority of the tests and more specific criteria. In 2016, the American Academy of Pediatrics published a clinical practice guideline detailing management according to risk categories, suggesting that some patients are at lower risk, based on age (older than 2 months), lack of prematurity (born at ≥ 32 weeks gestation), absence of previous episodes (first BRUE) or other concerns from history and physical examination. According to these recommendations, such lower-risk BRUE infants require minimal management: the physician should offer resources for training in cardiopulmonary resuscitation to the caregiver and may test for pertussis, a record 12-lead ECG and briefly monitor patients with continuous pulse oximetry and serial observations [9]. This approach was discussed recently in the Journal of the Swiss Society of Paediatrics, where it was suggested that lower-risk BRUEs are rare and that guidance on higher-risk BRUE and ALTE is insufficient [11]. Published data on the epidemiology and management of BRUE patients in Switzerland is, however, lacking. The aim of this study was therefore to determine the frequency of lower-risk BRUE and detail clinical practice and management.

Materials and methods

All cases of children with the diagnosis of a BRUE or ALTE admitted to our institution between September 2009 and April 2018 were identified using the International Classification of Diseases German modification (ICD-10GM) code R06.80. Electronic health records were used to extract the epidemiological and clinical data, as well as investigations performed. The clinical data were reviewed to verify the correct assignment of the ICD-10GM code. For the analysis infants were categorised according to previously published definitions as having a lower-risk BRUE: children older than 60 days but younger than one year of age, born at ≥ 32 weeks gestational age and post-conceptual age ≥ 45 weeks, first episode of BRUE with a duration of < 1 minute that resolved without cardiopulmonary resuscitation by trained medical providers and absence of concerning historical features or physical findings [9]. All children not fulfilling these criteria were categorised as having BRUE/ALTE.

Descriptive statistics were used to summarise groups and the use of diagnostic procedures. Data were compared using non-parametric testing (Mann-Whitney U-Test) and Fisher's exact test. Statistical analyses were performed using SPSS statistics software (IBM, Version 24).

The study was approved by the Ethics Committee of Northwestern Switzerland (2018-01224).

Results

We identified 65 admissions of 64 children with a median age of 42 days (interquartile range [IQR] 20–67) of whom 37/64 (58%) were male. The median duration of the event was 1 minute (IQR 1–2) and in 19/65 (29%) admissions the duration of the event was longer than 1 minute.

Premature birth < 32 weeks was present in 3/64 (4.7%) infants. A total of 10 cases (15%) fulfilled the lower-risk BRUE criteria and 4 were admitted after 2016 (table 2).

The median duration of admission was 72 hours (IQR 48–72) hours, with lower-risk BRUE children having a shorter duration of admission (48 hours, $p < 0.05$) (table 3).

Table 1:
Comparison of definitions of ALTE and BRUE.

	Lower-risk BRUE	Higher-risk BRUE	ALTE	Not BRUE or ALTE
Year definition started to be used	2016 AAP	2016 AAP	1986 National Institutes of Health Consensus Conference on Infantile Apnea	NS
Age group	> 60 days and < 1 year	≤ 60 days	> 37 weeks GA at time of onset, described as predominantly in children < 1 year	NS
Prematurity	GA ≥ 32 weeks and PCA ≥ 45 weeks	GA < 32 weeks	Described as a risk factor	NS
Duration	"Brief and resolved" < 1 min; typically 20–30 s	"Brief and resolved" < 1 min	NS	≥ 1 min
Other	Normal vital signs; normal appearance; patient returned to his or her baseline state of health after the event after presenting ≥ 1 of: (a) cyanosis/pallor (b) absent, decreased or irregular breathing (c) marked change in tone (hyper- or hypotonia) (d) altered level of responsiveness	As in lower-risk but infants who do not qualify as lower-risk patients concerning personal and medical history or current age are, by definition, at higher risk	Treatable conditions associated with ALTE: gastrointestinal, neurological, respiratory, cardiovascular, metabolic, endocrine, others such as child abuse	Fever or recent fever, event consistent with GER, swallow dysfunction, nasal congestion, sepsis, meningitis, infections with RSV, influenza or pertussis, breath holding spells, hydrocephalus

AAP: American Academy of Pediatrics; ALTE: apparent life-threatening event; BRUE: brief resolved unexplained event; GA: gestational age; GER: gastro-oesophageal reflux; NS: not specified, PCA: post-conceptual age; RSV: respiratory syncytial virus

Baseline characteristics of lower-risk BRUE and BRUE/ALTE infants were comparable except for age and duration of the event, which are part of the definition of lower-risk BRUE (table 2).

Overall, the following signs were reported at admission in the 65 admissions: 55 (85%) irregularities in breathing, 47 (72%) marked changes in muscle tone, 25 (38%) cyanosis and 14 (25%) pallor. The following diagnostic procedures were performed: full blood count in 56 (86%), C-reactive protein measurement in 49 (75%), cranial ultrasound in 41 (63%), urinalysis 24 (37%), polysomnography in 17 (26%), echocardiography in 15 (23%), electrocardiogram 51 (78%), nasopharyngeal swab testing for respiratory viruses in 13 (20%) (table 3). The majority of investigations were performed with equal frequency in the lower-risk BRUE and the BRUE/ALTE groups. The two exceptions were ophthalmology review and echocardiography, which were only performed in BRUE/ALTE infants, in 7/55 (13%) and in 15/55 (27%) cases, respectively (table 3).

The following abnormal results were reported: thrombocytosis 6/56 (11%), neutropenia 1/56 (1.8%), leucopenia 1/56 (1.8%) and leucocytosis 1/56 (1.8%) in the full blood count; acidosis in 4/61 (6.5%) in blood gas analysis; alterations in urinary amino/organic acids in 12/30 (40%); detection of rhinovirus 3/13 (23%) and respiratory syncytial virus (RSV) 2/13 (15%) in the nasopharyngeal swab; patent foramen ovale 2/15 (13%), patent ductus arteriosus 1/15 (6.6%), ventricular septal defect in 1/15 (6.6%) and physiological pulmonary stenosis in 1/15 (6.6%) with echocardiography; QTc prolongation in 1/51 (2%) and an incomplete right bundle branch block in 1/51 (2%) with electrocardiogram; hemispheric asymmetry in 3/28 (10.7%) and 1/28 (3.6%) unspecific increased susceptibility to seizures with EEG; a discretely dilated lateral ventricle in 1/41 (2.4%) and intraventricular haemorrhage in 1/41 (2.4%) on cranial ultrasound; 1/17 (5.8%) unclear desaturation episode for 20 minutes with polysomnography. In addition, during admission further clinical conditions were described: upper respiratory tract infection 5/65 (8%), gastro-oesophageal reflux 10/65 (15%).

Only one patient with a QTc prolongation was considered to have a serious underlying condition as a potential cause for the BRUE. The patient had no further episodes during admission and no explanation was found for the initial QTc prolongation, such as medication or electrolyte abnormalities. A follow-up 2 days after discharge showed normalisation of the QTc interval.

Previous medical history was remarkable for one child with a pertussis infection diagnosed and treated with antibiotics 2 weeks prior to the admission and one child with grade IV intraventricular haemorrhage on the left side and a grade I intraventricular haemorrhage on the right side.

One infant was readmitted 2 weeks after the initial presentation with a repeat BRUE. This infant qualified as BRUE/ALTE at both admissions because of age below 60 days and also because the second episode lasted longer than 1 minute. The work-up at the second admission consisted of an additional EEG, echocardiography, cerebral ultrasound and urine analysis including amino/organic acids. None of the results was abnormal.

Discussion

This is the first study in Switzerland evaluating the epidemiology and management of infants with a BRUE or ALTE during the time of changing definitions. We included patients from the time before the BRUE definitions were used in our institution and therefore used both ALTE and BRUE to identify patients for the study. However, as no patients were older than 1 year all included patients would now classify as having a BRUE. Of note is that, retrospectively, 15% of the patients in our study met the criteria for lower-risk BRUE, which according to the recent recommendations by the American Academy of Pediatrics would not qualify for hospital admission and further investigations. The analysis of the patients with lower-risk BRUE shows that all infants had blood sampling for blood gas analysis, the majority also had blood testing of full blood count and C-reactive protein, as well as an ECG. Further investigations were rarely performed. In the lower-risk BRUE infants, no concerning or severe underlying

Table 2:
Baseline characteristics of lower-risk BRUE and BRUE/ALTE patients.

	All		Lower-risk BRUE		BRUE/ALTE		p-value	
		%/IQR		%/IQR		%/IQR		
Total number	65	100	10	15	55	85	–	
Median age (days)	42	20–67	90	83–96	39	17–50	<0.001	
Number female sex	28	43	4	40	24	43.6	0.56	
Number preterm (< 32 weeks) births	3	4.6	0	0	3	5.4	0.64	
Number prior BRUEs	1	1.5	0	0	1	100	0.85	
Duration of BRUE (minutes)	1	1–2	1	1–1	1	1–3	<0.05	
Number CPR required	1	1.5	0	0	1	1.8	0.85	
Concerning history	1	1.5	0	0	1 ^a	1.8	0.85	
Concerning findings	1	1.5	0	0	1 ^b	1.8	0.85	
Nationality	CH	40	61.5	6	60	34	61.8	
	DE	6	9	0	0	6	10.9	
	FR	1	1.5	0	0	1	1.8	
	Other	18	28	4	40	14	25.5	

ALTE: apparent life-threatening event; BRUE: brief resolved unexplained event; CPR: cardiopulmonary resuscitation; CH: Switzerland; DE: Germany; FR: France

Data are presented as median with IQR (Interquartile range) or % of absolute numbers.

^a Prior ALTE/BRUE

^b QTc prolongation

causes were identified, and no readmission occurred. This finding is in line with the recommendation of the American Academy of Pediatrics and suggests absence of severe underlying diseases in the majority of children with a lower-risk BRUE [9].

A similar study done in Lombardy (Italy) between 2006 and 2016 found a comparable number of admitted lower-risk BRUE patients of 19% of 84 children [12]. In contrast, a study from New York (US) found only one patient with a higher-risk BRUE and none with a lower-risk BRUE among 78 patients seen for an ALTE, which was before publication of the BRUE guideline [13]. In their population, for 62% of infants the event was not resolved and for 94% of the cases the authors concluded that the event was not unexplained, but the final diagnoses of the infants was not specified. A further study in Charlottesville (US) between 2013 and 2016 included 87 infants with ALTEs of which 23% met the criteria for a BRUE and none for a lower-risk BRUE [14]. The discrepancy between US and European studies may be because there is a lower likelihood of presenting to emergency departments in Europe and lower admission thresholds in Switzerland and Italy.

In the group of the BRUE/ALTE infants, our data show a large variability in the investigations performed. In addition, there were many abnormal results recorded that however did not lead to identification of a serious underlying condition and therefore may have led to overdiagnosis and treatment. This is likely the result of the lack of guidance in the Swiss recommendations on the priority of investigations that should be performed. As shown in a system-

atic review, significant variation can be seen in diagnostic work-up and admission rates for patients with an ALTE [8]. A standard broad approach to testing and management of all patients with a BRUE/ALTE is not reasonable and more recent publications suggest a tiered approach with the priority being identification of conditions for which delayed diagnosis or treatment could impact outcome [15]. A careful and thorough history and physical evaluation remains the mainstay to guiding further investigations. Evaluation for maltreatment / child abuse, feeding problems, cardiac arrhythmias, infections (mainly sepsis, meningitis, and urinary and respiratory infections including pertussis), and congenital abnormalities is required. The recommendations suggest a minimum of 4 hours of continuous pulse oximetry monitoring, bedside feeding evaluation, an ECG read by a paediatric cardiologist, rapid viral nasopharyngeal swab testing, rapid pertussis nasopharyngeal swab testing during outbreaks or in under-immunised infants/mothers, and a very limited laboratory evaluation including haematocrit, a venous blood gas analysis and lactate [15]. Both the ECG read by a paediatric cardiologist and the rapid nasopharyngeal swab testing may be limited by availability of resources or the longer turn-around time in many settings, and therefore admission for 24 hours seems a reasonable approach.

We found that on average lower-risk BRUE patients were admitted for 48 hours and BRUE/ALTE patients for 72 hours with no further events occurring and only one patient requiring readmission. It is therefore debatable if admission of BRUE/ALTE patients with 48–72 hours monitoring

Table 3:
Comparison of investigations of lower-risk BRUE and BRUE/ALTE patients.

			Lower-risk BRUE		BRUE/ALTE		p-value
	n	%	n	%	n	%	
Total number	65	100	10	15	55	85	–
Blood sample	63	97	10	100	53	96	0.71
Full blood count done	56	86	8	80	48	87	0.42
– Abnormal results	10	18	1	13	9	19	0.52
C-reactive protein done	49	77	8	80	41	75	0.53
– Abnormal results	0	0	0	0	0	0	–
Blood gas analysis done	61	94	10	100	51	93	0.50
– Abnormal results	4	7	0	0	4	8	0.50
Urinalysis done	24	37	4	40	20	36	0.55
– Abnormal results	0	0	0	0	0	0	–
Nasopharyngeal swab done	13	20	2	20	11	20	0.64
– RSV positive	2	15	0	0	2	18	0.64
Echocardiography done	15	23	0	0	15	27	<0.05
– Abnormal	5	33	0	0	5	33	0.42
Electrocardiogram	51	78	8	80	43	78	0.63
– Abnormal	2	4	0	0	3	7	0.71
Ophthalmology review	7	11	0	0	7	13	0.29
– Abnormal	0	0	0	0	0	0	–
Polysomnography	17	26	2	20	15	27	0.48
– Abnormal	1	6	0	0	1	7	0.92
Urine amino/organic acids screening tests	30	46	4	40	26	47	0.47
– Abnormal	12	40	3	75	9	35	0.28
Cranial ultrasound	41	63	5	50	36	64	0.28
– Abnormal	3	7	0	0	3	8	0.59
Electroencephalogram	28	43	6	60	22	40	0.20
– Abnormal	4	0	0	0	4	18	0.50

ALTE: apparent life-threatening event; BRUE: brief resolved unexplained event; RSV = respiratory syncytial virus

Data are presented as n (%); lower-risk BRUE and BRUE/ALTE groups were compared using a Fisher's exact test.

is justified (as suggested in the 2007 Swiss recommendation). Evidence shows that more than a decade ago the average length of stay for an ALTE was 4.4 days [16] but in more recent studies much shorter durations of admissions of 20–28 hours are reported [14]. The vast majority of infants do not need interventions [17, 18] and a recent meta-analysis found the risk of death after a lower-risk BRUE to be the same as the baseline risk in the overall population during the first year of life [19]. There is little evidence to guide which BRUE/ALTE infants are most likely to benefit from hospital admission and most recent US recommendations advocate 4- to 24-hour monitoring and co-ordinated outpatient care to complete further non-urgent investigations [15].

A potential limitation of our study is its retrospective nature, which did not allow information on follow-up, whether further events not requiring admission had occurred, to be obtained. Furthermore the small sample size of 64 patients impedes the ability to detect rare diagnoses. In addition, our study included only admitted patients, as those managed in the emergency department only cannot be identified by the hospital's ICD-10GM coding system. It may be possible that further patients with a lower-risk BRUE were not included as they were managed as outpatients.

In conclusion, our data show that 15% of the admitted BRUE/ALTE infants can be categorised as lower risk and therefore hospital admissions and investigations can be reduced. Extensive investigations and two to three day admissions only rarely led to identification of an underlying severe condition, and shorter duration of admission and more individualised work-up may be possible. The adaptation of Swiss recommendations for BRUE and ALTE would be helpful in guiding national management.

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