In the past, BRUE was known as an apparent life-threatening event. Per this definition, one can conclude that BRUE is a clinical manifestation rather than a true diagnosis and a variety of conditions might lead to BRUE. Causes for BRUE can be identified and, thus, be treated accordingly. SIDS, on the other hand, is defined as the sudden death of an infant without an apparent cause per history and where a complete physical examination does not reveal a clear cause for the death.

Background and Definitions

Brief resolved unexplained event

Brief resolved unexplained event (BRUE) is diagnosed when an infant who is younger than one year of age experiences one of the main BRUE symptoms which include:

- Cyanosis or pallor
- Absent, decreased or irregular breathing
- Altered responsiveness
- Marked change in tone (hypertonia or hypotonia)
The duration of any of the BRUE symptoms should be less than 1 minute to be considered as brief. BRUE is considered as a near-death experience of infants and is usually a cause of excessive worry by the caregivers.

In the past, BRUE was known as apparent life-threatening event (ALTE). Per this definition, one can conclude that BRUE is a clinical manifestation rather than a true diagnosis. It is a diagnosis of exclusion when there is no explanation for a qualifying event after taking history, carrying out a physical examination and doing necessary tests. A variety of conditions might lead to BRUE.

Sepsis may be considered if there is fever or persistent respiratory symptoms such as cough, cyanosis, and nasal congestion.

Seizures may indicate epileptic attacks or central nervous system infection or anomalies.

Major trauma such as child abuse may be considered when the event history is reported inconsistently, or is incompatible with the child’s developmental age, or when there is unexplained bruising on physical examination more so on the genitals.

Congenital anomalies

Inborn errors of metabolism

Severe respiratory disease may also lead to BRUE in infants.

A cardiac arrhythmia may be considered if there is a family history of sudden, unexplained death in first-degree relatives.

Patients presenting with BRUE are then classified into:

- High-risk patients who require further workup and monitoring
- Low-risk patients who do not need workup or monitoring. The low-risk group is made up of infants with the following features:
  - More than one month of age
  - Premature infants
  - First BRUE episode
  - Duration of the BRUE event < 1 minute
  - No CPR required by trained medical provider
  - No features on history that would explain the event
  - No concerning features on physical examination

Sudden infant death syndrome

The National Institutes of Health has put a standardized and clear definition of sudden infant death syndrome (SIDS). SIDS is defined as the sudden death of an infant without an apparent cause per history, and where a complete physical examination does not reveal a clear cause for the death. The most recent definition of SIDS has limited the diagnosis to infants younger than one year of age, like BRUE. Most cases die during sleep; thus, it is sometimes known as crib death or cot death.

Epidemiology of Brief Resolved Unexplained Event
and Sudden Infant Death Syndrome

The estimated incidence of SIDS in the United States is around 0.57 per 1000. On the other hand, SIDS is much rarer in Japan for unknown reasons with an estimated incidence of 0.09 per 1000 infants. Ethnic differences in the incidence of SIDS exist in the United States. Native Americans seem to have the highest incidence of SIDS, i.e., 4 per 1000. African Americans also have a higher incidence of SIDS compared to white infants.

On the other hand, the estimated incidence of BRUE or apparent life-threatening events in infants younger than 1 year is around 4.1 per 1000; therefore, the incidence of BRUE is apparently higher than the average incidence of SIDS in the United States when ethnic differences are not accounted for.

The main risk factors for BRUE were gastroesophageal reflux disease, family history of BRUE or SIDS, and acute respiratory infections such as pertussis or bronchiolitis, according to a recent study. In another recent study, a true correlation between BRUE and SIDS was not found; hence, suggesting that while a family history of SIDS is a risk factor for BRUE, a previous history of BRUE in an infant does not put that infant at an increased risk of SIDS.

Risk Stratification and Classification of Brief Resolved Unexplained Event and Sudden Infant Death Syndrome

Brief resolved unexplained event

Risk stratification in BRUE is very important as it can help the clinician determine who needs to be admitted to the hospital and who can be discharged home safely from the emergency department.

For the infant to be considered as low-risk, all the following criteria need to be met:

1. Age > two months
2. Gestational age at birth above or equal to 32 weeks
3. No previous history of BRUE
4. Duration of BRUE symptoms less than 1 minute
5. Cardiopulmonary resuscitation was not needed to revive the infant, and history and physical examination do not point towards a serious or life-threatening condition such as sepsis
Infants who are diagnosed with low-risk BRUE should be monitored at the emergency department for 1–4 hours with pulse oximetry and serial check-ups on their vital signs and symptomatology. The diagnostic criteria for BRUE are strict and should be followed for the adequate classification of the patient. The infant’s age should be below 1 year, the clinician should be involved in the characterization of the event’s features, and the patient needs to have one of the following symptoms:

- Episodic pallor or cyanosis
- Breathing irregularities including apnea
- Hypotonia or hypertonia
- An altered level of consciousness characterized by poor responsiveness or unresponsiveness

Choking and gagging are not part of the diagnostic symptoms of BRUE per these criteria.

Sudden infant death syndrome

The main risk factors for SIDS can be classified into modifiable extrinsic risk factors and non-modifiable intrinsic risk factors.

The modifiable extrinsic risk factors include:

- Sleeping in prone position
- Soft bedding
- Sharing bed with parents
- Parental smoking
- Parental use of ethanol
Drug use by parents

A low socioeconomic status has also been described as a risk factor for SIDS.

The intrinsic risk factors include:

- Male gender
- Some polymorphisms on the gene encoding for the promotor region of the serotonin transporter
- Being black or Native American

Other non-modifiable risk factors include prematurity and perinatal exposure to smoking.

Recent studies have showed that the most common cause of SIDS is asphyxia which could be due to bed sharing with adults, or sleeping in the prone position.

The Five Steps Pathway and the Pathogenesis of Sudden Infant Death Syndrome

Early human and animal studies have showed that the most important cause of SIDS is asphyxia. Cardiorespiratory recordings in infants who died from SIDS afterwards and animal experimental studies have pointed towards a five-step pathway in the pathogenesis of SIDS.

1. The first step is a life-threatening event which causes either severe asphyxia or severe brain hypoperfusion. This step can happen in any infant and most infants recover from it. When the asphyxia is severe enough, the infant might fail to wake up, or turn his or her head into a better position.
2. This can be related to the severe hypoxia and hypercapnia seen in patients who progress to the second step after asphyxia.
3. The infant will then develop severe progressive asphyxia, will lose muscle tone, and will enter a hypoxic coma.
4. If no intervention is made by the caregiver so far, the infant is expected to enter the fourth step where extreme bradycardia and gasping ensue.
5. This is a terminal event that usually happens before the last step which is characterized by failed auto-resuscitation and eventually death.
Diagnostic Workup in Brief Resolved Unexplained Event and Sudden Infant Death Syndrome

Sudden infant death syndrome

Any infant who is brought to the emergency department with sudden unexplained death should only be diagnosed to have died of SIDS after:

- Examination of the scene and circumstances around the death of the infant.
- **Detailed history should be obtained** from the caregiver on the medical background of the infant and close family members.
- If no cause can be identified, an autopsy should be performed to exclude any apparent cause for death, preferably by an experienced pediatric pathologist.

When the autopsy fails to reveal the cause of death, the diagnosis of SIDS is confirmed.

Brief resolved unexplained event

Diagnostic workup in infants with BRUE should be **tailored towards the most likely cause and the risk stratification** of the infant.

**Low-risk infants** without any apparent cause should not receive any extensive testing except for a **continuous pulse oximetry monitoring**, combined with serial **vital signs check-ups** while at the emergency department for **four hours** to be later discharged home.

**In high-risk infants**, the cause of the BRUE presentation can usually be determined from the **history and physical examination**. In that case, laboratory investigations, imaging studies and any more specific tests should be performed as per the **routine diagnostic workup for the cause of the BRUE**; therefore, there are no specific tests to be performed to confirm the diagnosis of BRUE.

Treatment of Brief Resolved Unexplained Event and Sudden Infant Death Syndrome

Brief resolved unexplained event

The treatment of low-risk BRUE is merely **close observation at the emergency department** for four hours followed by discharge with some advice and recommendations.

The nature of the event, the possible causes, and its association with SIDS should be explained to the caregivers or parents.

High-risk BRUE should be treated in an inpatient setting with close monitoring. **No specific treatment is indicated** for the BRUE itself, but **antibiotic therapy** for an acute respiratory infection, or anti-reflux treatment for gastroesophageal reflux disease are indicated when needed.
Sudden infant death syndrome

There are a few measures that have been proven to lower the risk of SIDS and they include putting the infant in the supine position in a shared room but a separate bed with a firm mattress.

During pregnancy, the mother should be encouraged to stop smoking if she is a smoker. Over-heating of the room, bed sharing, soft bedding, prone sleeping and side sleeping should all be discouraged.

If SIDS occurred, professional grief counseling with an experienced psychologist is required. The unexplained sudden death of an infant can trigger feelings of anger and guilt which can later lead to depression or anxiety.

References


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