Sudden Unexplained Death in Childhood
Current Understanding

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Abstract: Sudden unexplained death in childhood is a term that encompasses apparently natural deaths in children aged older than 1 year with no discernible cause despite a thorough assessment. Definitive underlying causes vary but most cases remain largely unexplained. Research has furthered the view that sudden unexplained death in childhood is not an accident, but rather a sentinel medical event for which a thorough postmortem investigation is indicated. Emerging evidence in genetics, neurology, and neuropathology point to heterogeneous causes that in some cases share features of recognized diseases.

Key Words: sudden unexplained death in childhood, sudden unexpected death in epilepsy, sudden infant death syndrome, infant mortality

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TARGET AUDIENCE

This CME activity is intended for all practitioners who care for pediatric patients aged older than 1 year who die suddenly and unexpectedly, which may include: pediatricians, general practitioners, pediatric emergency physicians, general emergency physicians, and pediatric intensive care physicians.

LEARNING OBJECTIVES

After participating in this activity, the learner should be better able to:

1. Define sudden unexplained death in childhood (SUDC) and discuss the latest related genetic findings.
2. Discuss the frequent relationship of SUDC to seizures that are often febrile.
3. Identify neuropathologic findings associated with SUDC.
4. Describe the relationship between SUDC, sudden infant death syndrome (SIDS), sudden unexplained cardiac death, and sudden unexpected death in epilepsy (SUDEP).

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The sudden, unexplained death of a child aged older than 1 year is a conceptual "no man's land" for pediatrics. Although it has long been appreciated that a small number of children who are no longer infants die under circumstances similar to SIDS,[1,2] their deaths seem to violate an established view that SIDS is preventable and its risk can be outgrown. The phrase *sudden unexplained death in childhood* was coined before prone sleep position of infants was identified as a risk factor for SIDS,[3] yet the rarity of the mortality coupled with the attention provided to SIDS have served to obscure it. The modern era of research on SUDC began with a report of 50 cases in 2005 from the San Diego SUDC Research Project.[4] Since then, research on SUDC has yielded consequential insights, with implications for SIDS, epilepsy, cardiology and, in the pediatric emergency medicine setting, the management of febrile seizures. What has remained constant is the difficulty of communicating and providing early guidance to bereaved parents and families experiencing acute loss and overwhelming grief.

DEFINITIONS

Unexplained deaths in children aged older than 1 year were originally included in the definition of SIDS, which initially encompassed the sudden death of *any infant or young child* unexpected by history.[5] When the definition of SIDS was restricted to younger than 1 year,[6] unexplained child deaths occurring after infancy lost their diagnostic designation. For more than a decade, this lack of any common definition impeded surveillance and research. This vacuum was addressed in 2005, when Krous proposed a definition for SUDC: the sudden death of a child aged older than 1 year that remains unexplained after a thorough case investigation, including review of the clinical history and circumstances of death, and the performance of a complete autopsy with appropriate ancillary testing.[4]

This definition of SUDC paraphrases the SIDS definition,[7] and its diagnostic category is understood as a diagnosis of exclusion that describes the failure of comprehensive efforts to find an explanation in an ignored pediatric age group. Although this definition became the general framework under which research could proceed, it is not universally adopted, and cases more consistent with SUDC are often found in research concerned with other diagnoses (Table 1). As an example, in a recent study of sudden cardiac deaths in children and young adults, 10% of the unexplained cases were aged between 1 and 5 years (mostly between 1 and 2), had normal autopsies with structurally normal hearts, and 91% died during sleep,[10] that is, SUDC in all but name. This variable accounting reflects the broadness of the definition of SUDC and that clinical details for these deaths often amount to no more than that these are "normal" children whose hearts stop or who experience irreparable brain injury for inapparent reasons.

Sudden unexplained death in childhood cannot be diagnosed in an emergency department. From the perspective of emergency health care workers confronting these tragic deaths, it is important to differentiate between the terms *unexpected* and *unexplained*.

TABLE 1. Definitions*

Sudden Unexplained Death in Childhood (Krous et al, 2005)
The sudden death of a child aged older than 1 y that remains unexplained after a thorough case investigation, including review of the clinical history and circumstances of death, and performance of a complete autopsy with appropriate ancillary testing.

Sudden Death in the Young (Burns et al, 2017)
The sudden and unexpected death of a child aged younger than 20 y, excluding deaths, which during autopsy or initial investigation, are attributed to an accident, homicide, suicide, accidental or intentional overdose of drugs, terminal illness.

SUDEP (Nashef et al, 1997)
Sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning deaths in patients with epilepsy, with or without evidence of a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death

Unexplained sudden cardiac death (Bagnall et al, 2016)
Sudden cardiac death for which no cause was identified after a complete and comprehensive autopsy examination that included histologic and toxicologic studies.

Sudden Unexpected Death in the Young (Behr et al, 2020)
A witnessed, nontraumatic, and unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy individual or an unwitnessed death that occurred in the 12–24 h before the individual last being seen in good health.

*There is general agreement about the definition of SUDC.[4] However, SUDC cases are often found in studies classifying the case otherwise, including sudden death in the young,[8] SUDEP,[9] sudden unexplained cardiac death,[10] and sudden unexpected death in the young.[11]

When a deceased child presents to an emergency room without an apparent cause for their death, the death would be characterized as *unexpected*. If no cause of death is ascertained after a thorough review of the medical history, death scene investigation, and complete autopsy, the child's death would be considered *unexplained*. For example, unexpected child deaths may ultimately be found to be caused by infection or cardiac tumors,[12] and are thus unexpected but explained. Approximately 20% of unexpected pediatric deaths in children older than 1 year are ultimately explained after a complete autopsy,[4,13,14] with causes ranging from complications of acute infections (including myocarditis, pneumonia, or encephalitis), diabetes, cancer, and congenital anomalies.[15] Not uncommonly, minor pathologic findings are identified that do not rise to the level of cause and thus the deaths are considered unexplained.

EPIDEMIOLOGY

The International Classification of Diseases has no entry for SUDC.[16] This absence of endorsed terminology impedes uniform death certification and reporting, and it also leads to definitional vagaries that affect estimates of its incidence. Most reports of the incidence of SUDC rely on codes included under the parent ICD classification of "ill-defined and unknown causes of mortality" in children aged 1 to 17 years. Accordingly, in 2020, 429 US children aged between 1 and 18 years died due to SUDC (0.6 deaths/100,000 births or 3.0% of child mortality between 1 and 18 years), with 34% occurring in the second year of life. The incidence of SUDC peaks at age 1 to 4 years, with a mortality rate of 1.3/100,000 live births, and subsequently decreases until a nadir in the 10th year with a rise thereafter, in parallel with overall mortality patterns. There has been little change in SUDC mortality rates over time: the 1990 mortality rate in 1- to 4-year-olds was 1.5/100,000.[17]

Sudden unexplained death in childhood is rare, even by pediatric standards. By comparison, the US mortality rate for sudden unexpected infant deaths, encompassing SIDS, deaths of undetermined cause, and accidental suffocation in bed, is 102.1/100,000 live births. For SIDS alone, the mortality rate is 37.2/100,000.[18] The relationship between SIDS and SUDC is an important concern. Are infant deaths avoided by "safe sleep practices" delayed or prevented? The answer is complex, but a provocative—though unreplicated—study from Ireland found that the SIDS rate dropped by 52% over a 12-year period, whereas the SUDC rate increased by 124%.[13] At this point, any link would be speculative, although there are a growing number of links between SUDC and SIDS helping define the former and redefine the latter. In general, research in this area is limited by retrospective, convenience samples and nonuniform sampling of tissue.

Efforts to gain specificity in the phenotype begin with Krous's "SUDC profile," characterized by the children being aged 1 to 3 years, predominantly male, and frequently having a personal and/or family history of seizures that were often febrile.[4] The SUDC deaths are largely associated with sleep, but not uniformly. Most children are found prone, often with their face straight down into the sleep surface. Most are sleeping alone. There are some reports that the deceased child was more likely to be found prone in SUDC than SIDS.[13] Among 1- to 4-year-olds, SUDC rates among non-Hispanic Black children were more than double those of white children, and most reported cases have been singletons born at term.[4,19]

CONSIDERATIONS RELATED TO SEIZURES

Although most cases of SUDC have been found in the prone position (72%[13] and 84%[14] in the larger published studies), developmental vulnerabilities in the motor strength of infants, often regarded as a critical feature in SIDS, would not seem to apply to this age group. Instead, similarities with SUDEP are likely of greater relevance, where the deceased are also typically found in the prone position and often face down.[14] In SUDEP, this is due to "forced ictal version" and postictal hypopnea.[20] In one SUDEP study, 5 of 7 "nonprone" patients transitioned to a "prone" position at the termination of the seizure, suggesting that the prone position in SUDEP may be more consequence than risk for death.[21] Indeed, the discussion about prone position in SUDC challenges assumptions underlying the vulnerability ascribed to 4-month-old infants (with limited motor development) found in the prone position in SIDS, and shed new light on early observations about apnea in SIDS.[22]

From the earliest reports, an important association between SUDC and febrile seizures has become apparent.[4,13,14,19] Febrile seizures are common, present in 2% to 5% of US children, with higher rates reported in Asian populations.[23] Although febrile seizures generally warrant reassurance, a personal history of febrile seizures has been identified in 31% in reported cohorts of children who die from SUDC, whereas no children who died suddenly with a reasonable explanation identified were found to have such a history.[14] Many children who have died from SUDC have a family history of seizures consistent with an autosomal-dominant inheritance pattern.[24] This pattern of inheritance is also seen in genetic epilepsy with febrile seizures plus (GEFS+) and familial febrile seizures, suggesting possible overlap that is survival-dependent. Mortality related to simple (≤15 minutes and no recurrence within 24 hours) febrile seizures is similar to that of the background population, whereas mortality is increased for complex (>15 minutes or recurrence within 24 hours) febrile seizures.[25] Although fever or illness were present in 75.6% of all SUDC cases, there was not a significant difference in antecedent

fever or illness symptoms within 48 hours of death in cases of SUDC with or without a history of febrile seizures.[26]

Further evidence suggestive of epilepsy and/or seizures in SUDC is found in neuropathologic studies (Fig. 1). Morphologic and histologic features seen in SUDC cases include developmental asymmetry of the hippocampus, characterized as external (morphological) asymmetry accompanied by microdysgenetic features.[29] This anomaly is present in 62% of all SUDC cases and 82% of SUDC cases with an individual/family history of febrile seizures.[19] Most significantly, in the largest neuropathological study to date, a hallmark of temporal lobe epilepsy,[30] bilamination of the granule cells in the dentate gyrus, was seen in 48% of SUDC cases, and of these, 63% had a personal or family history of febrile seizures.

GENETICS

Genetic investigations in SUDC involve small cohorts with heterogeneous findings, yet common substrates are suggested. A hereditary contribution to SUDC is supported by the observation of recurrent cases within families and the increased risk of SIDS/SUDC in the presence of a family history of such a death.[31] In practice, clinical genetic testing most frequently relies on panels of genes associated with a common phenotype that may cause sudden death, such as epilepsy, cardiomyopathies, or cardiac arrhythmias, due to cost limitations. Alternatively, research groups often take a hypothesis-free approach using exome sequencing or genome sequencing, in which genome-wide sequencing is performed and analyzed for potential causal variants. The purpose of such investigations is to uncover monogenic conditions that would explain these deaths, such as the finding of a pathogenic *RYR2* variant, associated with ventricular arrhythmia leading to SUDC in a recent cohort study.[32] For this study, trio exome sequencing was performed for 124 probands with SUDC and their parents and identified molecular genetic diagnoses in 11 cases, for a diagnostic yield of 9%.[32] Most diagnoses were de novo (7/11), but 3 inherited dominant variants and 1 autosomal recessive disorder were also identified.[32] The SUDC cases have been included as evidence illustrating that cardiomyopathy genes can cause death due to arrythmogenic tendencies before pathognominic tissue changes are apparent.[33] Others have identified deleterious variants associated with epilepsy (*SCN1A, GABRB3*) in children with a history of febrile seizures and family histories of epilepsy.[34,35] Causal variants have also been identified postmortem in children with physical signs consistent with syndromes implicated in the deaths (*ANKRD11, FLNA, BRPF1*),[35,36] although these syndromes remained undiagnosed while the child was living.

To date, genetic studies in SUDC have been limited to reporting known monogenic conditions and have elucidated important underlying diagnoses that were not suspected before death. However, as in most disease, these sequenced cases represent a minority of all cases of SUDC and have only scratched the surface of genomic contributions to this rare entity. In addition to extreme presentations of known diseases, SUDC may also occur as a result of as-yet-unrecognized conditions, potentially involving oligogenic processes or rare diseases incompatible with survival. In some centers, each case is an *n-of-1* effort in gene discovery.[37]

Advocating for genetic evaluation is valuable to provide an explanation to bereaved parents, and there may also be important implications for risk to asymptomatic or presymptomatic family members and siblings, with the potential for cascade testing of other family members at risk, depending on the condition identified.[38] An autosomal-dominant condition, in which the presence of a pathogenic variant on 1 allele is sufficient to cause disease, may either be inherited from a parent or may occur de novo in the affected individual. Although one might expect that an inherited dominant condition would not be seen in the case of presumably healthy parents who have a child with a lethal genetic condition, several autosomal-dominant genetic conditions may demonstrate incomplete penetrance, where not all individuals who carry the pathogenic variant manifest disease. For example, cardiomyopathies and genetic cardiac arrythmia syndromes may present in this fashion.[39] Interestingly, it is hypothesized that even for dominant conditions, cases presenting as sudden, unexpected death are more likely to demonstrate de novo inheritance—potentially reflecting the lethal nature of these variants, where survival into adulthood and reproductive fitness is diminished.[39]

MANAGEMENT

Emergency care often amounts to an intense but unsuccessful resuscitation effort while social services/child protective services work in the wings. Frequently, law enforcement is present. Whatever transpires, the ordeal for the parents, families, and caretakers does not end when the time of death is recorded. For those inclined to extend themselves, there is a role for clinicians to counsel the family, not only about the difficulties of child loss, but also about what will happen to their child—where the child's body will go, and what will happen to them (autopsy, return of the body)—and to prepare them for the scrutiny, including possible scene investigation, that is likely to follow. Support groups composed of families who have lost a child to SUDC can be extraordinarily helpful but, in the acute setting, clinical presence and careful counsel by those

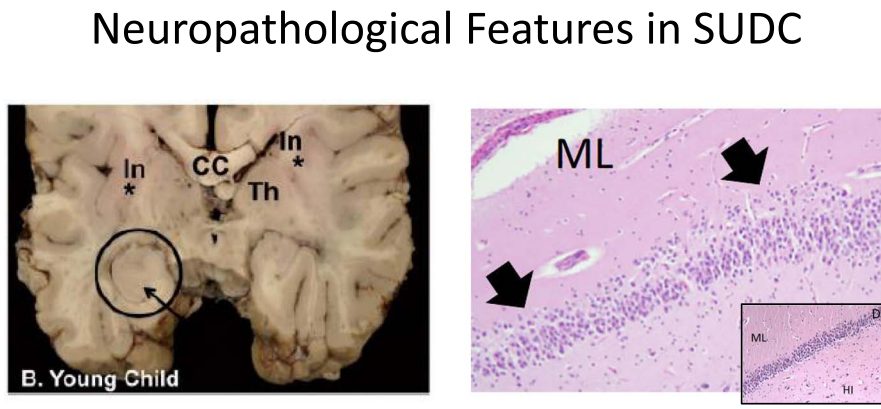

FIGURE 1. Described neuropathological features of SUDC include (A) asymmetry and malrotation of the hippocampus[27] and (B) bilamination of the granule cells in the dentate gyrus with normal inserted.[28] CC indicates corpus collosum; In, insula; Th, thalamus. Permission granted by authorship.

involved in the child's final medical treatments can have a unique role in a parent's understanding and their adaptation to the loss.

The most likely outcome is not that child protective issues will be discovered, but that medicine will fail to contribute to the family's understanding of this unfathomable event, while introducing distress in the process. It is worth emphasizing that parents and families typically derive comfort knowing what did NOT cause the death of their child. Clinicians should carefully consider this likelihood, and work to assure that the best possible outcome occurs both diagnostically and in terms of family coping. Early discussions with parents provide the opportunity to counterbalance the general lack of awareness about SUDC by explaining that, although rare, SUDC is a known cause of death. This counsel is especially helpful when clinicians avoid language that conveys hopelessness that an explanation will ever be found. Anecdotally, parents report finding some solace that there are efforts to understand more in this troubling area.

In addition to the diagnostic efforts that are routinely used when a patient presents in extremis, it is important to ask about a history of febrile seizures, epilepsy or other sudden deaths in the family, and make referrals for further assessment when warranted. Obtaining and processing of a "purple top," ethylenediamine tetraacetic acid (EDTA)-preserved tube of blood, to be available for genetic sequencing, is strongly encouraged. It is recommended that emergency medical staff bring up the array of possible diagnostic considerations with the parents, underscoring the importance of a thorough investigation while explaining that SUDC may well be the final cause of death, should diagnostic studies prove unrevealing.

It is helpful to consider the role of medical examiners and coroners in SUDC. This may include explaining to parents that the sudden unexpected and seemingly unexplained death of their child falls under their jurisdiction and, while they are legally authorized to perform an autopsy, that does not necessarily imply suspicion of wrongdoing. Proactive communication from medical staff involved in the terminal treatment of sudden unexpected deaths of children with the medical examiner can be extremely elucidating and is encouraged to achieve the optimal postmortem evaluation. Depending on community standards of practice, the limited resources of medical examiner offices might be mentioned to parents so as to adjust their expectations. It may be helpful to advise parents of the possibility of an independent secondary autopsy that includes assessment by pediatric pathologists, neuropathologists, and genomic sequencing (Unfortunately, the cost must often be borne by the family). In the long term, autopsy reports frequently arrive to the family's home unannounced and after considerable delays. Volunteering to review the report and explain findings is helpful. Importantly, incorporating awareness of the overwhelming impact of this loss on the family is critical.

There may be a tendency to leave matters to social services, who have important expertise in assessing and supporting a family. Yet, medical providers should assure that the parents become aware of the support that is available to them. Many parents describe being handed a stack of papers with resources they are unable to look at because they are so shattered by their loss and lack the heart to even touch the papers. It is important to help families find support groups and organizations that can help with their feelings of isolation, failure, and stigmatization. A follow-up phone call, a condolence note, or attendance at a memorial service are also efforts by clinicians that have meaning to families.

Special Mention About Febrile Seizures

On a population level, SUDC is an extremely rare event and febrile seizures are common. The power of a febrile seizure to predict future SUDC is very small, and reassurance for a benign outcome is generally a reasonable approach. Still, the consistent association between risk for SUDC and personal and/or family history cannot be ignored. We recommend asking about family history for SIDS, sudden unexpected infant deaths, and SUDC and believe that in cases where that is positive, the child should be referred to a neurologist.

SUMMARY

We review the epidemiology, pathology and pathophysiology, and current understanding of the etiologies of SUDC, a rare and neglected entity. Important inroads to understand the causes of SUDC have been gained through neuropathological findings that overlap with seizures, associations with febrile seizures, genetic variants associated with cardiac disease and epilepsy, novel variants, and undetected syndromes. Incorporation of postmortem genomic investigation has elucidated the underlying etiology in a small but critically important number of cases with implications for surviving family members. Systematic investigation into SUDC is needed to understand its medical basis and the risk it carries for other family members.

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