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Case Report

Fever as the Initial Sign of Febrile Seizure (Case Report); Febrile Seizure as a Cause of SIDS/SUDC; Suggested Steps for Early Recognition and Treatment Strategies

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Received: January 23, 2025; **Published:** February 11, 2025

Abstract

Sudden infant and childhood deaths are a catastrophic enigma since the cause is unexplained, even after careful investigation, and it remains a diagnosis of exclusion. It is proposed that febrile seizures may play a significant role in these deaths, and that a sudden spike in fever may be the initial manifestation of the seizure, which may be reflected by a rise in expression of heat shock protein. Further studies to confirm this observation and recognize structural, metabolic and genetic markers to identify those at risk are warranted. Special attention to assess risk following certain childhood vaccinations is also necessary. Even when medication to control fever is given, and the fever remains low-grade, a sudden spike in temperature can occur, which may be the first indication of seizure onset. If this observation is confirmed, an effective method to alert that a temperature spike is occurring is needed to facilitate rapid intervention of seizure control with rectal diazepam. The seizure may be sufficiently severe to cause death if untreated.

Keywords: *Sudden Infant Death Syndrome (SIDS); Febrile Seizure; Diazepam*

Introduction

Sudden unexplained infant and childhood deaths are characterized by the manner and age group in which they occur. Sudden infant death syndrome (SIDS), is death unexplained by investigation and/or autopsy occurring up to one year of age [1]. In contrast, sudden unexplained death in childhood (SUDC), is death unexplained by investigation and/or autopsy and occurring after one year of age [2]. The cause of death is not identified in either circumstance, and each remains a diagnosis of exclusion [3]. However, increasing evidence has accumulated to address a potentially primary role of febrile seizures in the causation of these deaths [4-6].

Febrile seizures were initially considered to be self-limited events, triggered by a sudden rise in body temperature [2,7-9], but further analysis has revealed their occurrence when recorded temperatures have been as low as 100.4F and above [10]. However, seizures manifesting as fever have been described [11]. In this case report, I propose the following possible setting:

1. A relatively low-grade temperature of 100.4F may be present for an undefined, variable period of time, and may be due to any one of a variety of causes;
2. In a susceptible individual, the low-grade fever lowers the seizure threshold via complex pathogenetic mechanisms [12,13];

3. Susceptibility may be a reflection of an underlying structural, metabolic, or genetic predisposition;
4. In this setting, a "febrile seizure" occurs, of which the first indication can be a sudden, non-linear, "spike" in body temperature;
5. If unsuspected, or undetected, a febrile seizure can lead to death by a variety of mechanisms, including: hypoxia, anoxia, cardiac arrhythmia, and hypotension.

SIDS/SUDC remains a horrifying and unexplained catastrophic enigma in clinical pediatric neurology. By definition, the cause of death in SIDS/SUDC is unknown [14]. Although a number of etiologies have been suggested, including an environmental source, such as a viral infection [15], or prior vaccination [16], autopsy findings have often been non-contributory regarding identification of a specific etiology [17]. This may reflect difficulty in identifying persisting detectable abnormal findings needed to discover the cause of death post-mortem.

In my opinion, the classification of these essentially identical conditions, SIDS and SUDC, based solely on age, represents a distinction without a difference. It places a higher priority on external factors, which takes the focus off other relevant factors, such as family history, identification of risk genes, and searching for subtle structural differences in relevant epileptogenic brain regions, such as the hippocampus.

For SIDS, alternative explanations, such as the previously proposed "The Triple Risk" model, suggests that a convergence of external factors (prone or side sleeping, overbundling, airway obstruction), a critical period of development (greatest between 1 - 4 months), and intrinsic vulnerability (dysfunctional and/or immature cardiorespiratory and/or arousal systems) is what leads to death [18].

For SIDS, this concept has focused more on suggestions for a safe sleep environment, including supine positioning on a firm, non-inclined sleep surface, avoiding overheating, breastfeeding, and use of a pacifier to reduce the risk of SIDS, which has been advocated by The American Academy of Pediatrics [18]. However, I propose that the role of febrile seizures in both SIDS and the etiology of the seizure disorder deserves further exploration.

Febrile seizures typically occur within the age range from 6 to 60 months, with a temperature of 100.4°F (38°C) or higher. Febrile seizures are not attributed to central nervous system infection or metabolic disorder, and first occur in the absence of a history of a previous seizure [19].

Febrile seizures are further characterized as simple, complex, and febrile status epilepticus. A simple febrile seizure is primary a generalized, tonic-clonic episode associated with fever, lasting a maximum of 15 minutes, and not reoccurring within a 24-hour period [8]. In contrast, a complex febrile seizure is longer (> 15 minutes), may be focal in nature, and may reoccur within a 24-hour window [20]. Febrile status epilepticus may be the child's first seizure, arbitrarily defined as lasting beyond 30 minutes [21].

It is now appreciated, but not yet fully incorporated into standardized treatment protocols and guidelines, that earlier and vigorous treatment of these seizures is essential to preserve brain function depending upon their duration and severity [22,23]. Additionally, fundamental questions regarding whether the seizure was a reflection of an underlying structural "lesion" [24-26], or "genetic" predisposition [27,28], by judicious investigation of pertinent family history of a seizure disorder [29], either of which could predispose to an ongoing seizure disorder, are addressed.

A significant issue regarding the current state of the art is reflected in the widely held perception that the vast majority of "febrile seizures" are self-limited conditions which typically are outgrown by the age of five [1-3,10]. Although there are individuals in whom febrile seizures are a benign, albeit frightening event, in other individuals, febrile seizures can be the harbinger of significant future morbidity, and even death. It is my intention, and sincere hope, to draw attention to this issue, and hopefully stimulate further studies

of this phenomenon. To do this, I will address a case history of a complex febrile seizure with a fortunate outcome. The patient received appropriate and immediate medical attention by good fortune alone.

Case History

A case report of a near-fatal febrile seizure in a 13-month-old, previously healthy male is reviewed. There was no prior history of any form of seizure activity. However, pertinent relevant factors include a three-and-a-half-month history of recurrent respiratory and ear infections, often with low grade fever (99.5-101.2F), attributed to repeated exposure in daycare, two days per week over that time period. He previously had been treated for an initial episode of acute otitis media with a full course of Amoxicillin, and for a separate second ear infection, Augmentin. He most recently completed a full course of the antibiotic Cefdinir (Omnicef) for a third ear infection two weeks prior to the febrile seizure.

Additional history is also pertinent. First, standard vaccinations were administered to this child at regular intervals, but a potential complicating factor was the recent administration of a combination of the MMR, Hepatitis A and Varicella vaccines given 9 days prior to occurrence of this first seizure, a complex febrile seizure. Recent vaccinations, the MMR (measles, mumps, and rubella) in particular, like the influenza and Tdap (tetanus, diphtheria and pertussis) vaccinations, have been associated with the post-vaccinal complication of febrile seizure [16]. There is a window of "risk" for such a reaction, which reflects the immune-inflammatory response of the individual to these vaccines, with a peak between 1-2 weeks, but can remain a concern for as long as 3 weeks [16].

Another relevant aspect of his medical history is that this child is an IVF baby, utilizing a donor egg. Although the genetic background and family history of the father was well known, and included genetic screening, the same was not applicable for the genetic background and family history of the egg donor. Although "screened" for inherited conditions, specific details of the genetic background of the egg donor are unavailable. Therefore, genetic screening of the child is necessary.

The child was taken to the pediatrician one day prior to the febrile seizure because he was running a low-grade fever once again, and was pulling on his ear. He was evaluated, cleared to go home, and the parents were advised to administer acetaminophen for a fever greater than 100.1F. This low-grade fever was attributed to teething. When the child was being readied for bed on the date of the febrile seizure, it was noted that he still had a low-grade fever of 100.1F despite receiving acetaminophen at regular intervals.

Acetaminophen oral suspension (120 mg/5 ml), had been administered in 3.75 ml (90 mg) aliquots at 4-6-hour intervals throughout the day, yet the fever persisted all day. Since the child was irritable and remained irritable during this time period, his temperature was checked again, and was 100.2F. Within ½ hour he felt very hot, and became listless. His temperature shot up to 103.2F within minutes, and when re-checked a second time reached 105.0F. His eyes then rolled up in his head and his extremities began to tremble in a tonic-clonic fashion. This was recognized as a generalized seizure, and he was rushed to the closest hospital, which fortuitously was just five minutes away.

When evaluated in their Emergency Department, he was actively seizing for 20 minutes, observed to be intermittently apneic, and was noted to have a pO_2 of 70% utilizing a pulse oximeter on the finger, and as low as 50% on a direct blood gas measurement. His heart rate was as high as 194 on the cardiac monitor. The seizure activity lasted 20 minutes, and was therefore defined as a complex febrile seizure. It was controlled by administering two doses of midazolam, and he was post-ictal over the next two hours. He also received rectal acetaminophen which rendered him afebrile. He was treated with Ceftriaxone for acute otitis media, and additional doses of acetaminophen or ibuprofen during the remainder of the night were administered to control his fever. He remained afebrile in the hospital, and recovered uneventfully overnight. He was sent home the next day.

Discussion and Conclusion

Five points need to be made.

First, had this child been given acetaminophen and placed in the crib for the night, with the low -grade fever he had all day, the complex seizure he suffered was of sufficient severity to cause death if untreated. He required effective and urgent treatment. A more effective method of managing this issue would be periodic monitoring of his temperature throughout the day or night. An effective method to alert that a temperature spike is occurring is needed to facilitate rapid intervention of seizure control with rectal diazepam.

Second, the sudden escalation in fever and subsequent complex febrile seizure was not predictable, and had the child died at home in bed, the sudden unexplained death due to seizure would likely have been undiagnosed. The death would likely have gone unexplained, which is a cardinal feature of SIDS/SUDC [30].

Third, MRI and genetic studies are warranted. The MRI is to determine whether there were structural aberrations that contributed to, or were caused by the seizure activity. There is evidence that there are subtle hippocampal lesions in some individuals who subsequently develop febrile seizures [31]. Furthermore, there is also evidence that children with febrile seizures may be found to have acute lesions in the hippocampus, which may also predispose them to further febrile seizures, or even epilepsy [32,33]. This issue requires further research because it is a chicken-egg issue at best at this time. Nevertheless, these are objective findings which deserve further analysis.

Genetic studies are performed to identify whether there are genetic factors that influenced susceptibility to further seizure activity. Multiple gene loci have been identified in individuals with both epilepsy, and specifically, febrile seizures [13]. This information is relevant to identify the most effective course of treatment.

Additionally, further investigation of biological markers. Elevation of heat shock proteins, for example, may prove useful as a tool in corroborating the suspicion that a febrile seizure has occurred.

Fourth, consideration of the effects of the role of vaccination [16], its composition and dose are needed. Repeating reduced dosing and protocols separating individual vaccinations are worthy alternatives to allow vaccination, yet reduce risk of post-vaccination complications [16], such as a febrile seizure. Further studies of these issues are also warranted.

Fifth, the widely acknowledged abrupt rise in body temperature has been considered a trigger of the seizure [7]. Instead, I propose that this fluctuation is actually the initial manifestation of the seizure, analogous to the aura in migraine. While administration of an antipyretic agent, such as acetaminophen is considered effective [34], breakthrough seizures do occur, such as in the present case report. Although possibly considered extreme, perhaps rectally administered diazepam [35], should be prescribed to have available in the event of a febrile seizure, with instructions for its use, for children with recurrent febrile illness, such as otitis media, or febrile reactions to vaccination. In the same vein, I would also encourage daycare facilities to be knowledgeable in the administration of this medication. This would be akin to having an epi-pen available for treating anaphylaxis in individuals with hypersensitivity to bee stings, peanuts, and other potential allergens.

In summary, a case report of a 13-month-old, previously healthy male is presented. The child had recurrent bouts of upper respiratory infections and otitis media, some accompanied by fever. He received at least three separate courses of antibiotics and acetaminophen, with complete resolution of the infection and fever on each occasion. During the fourth episode, his fever persisted, low-grade, despite receiving acetaminophen at regular intervals while febrile. He then spiked a fever of 105.0F and manifested a tonic-clonic seizure lasting over 20 minutes. This was characterized as a complex febrile seizure. He became severely hypoxic during this seizure. Had he been left in his crib, without closely monitoring his temperature, and seeking timely emergency care this sudden onset seizure could likely have

caused death. Confirmation of seizure activity may be documented by finding elevated levels of heat shock protein 70 (HSP-70), which can be detected postictally [36], and perhaps even post-mortem.

This framing of the pathogenesis of SIDS/SUDC, in which other etiologies have been eliminated, and the cause of death remains unexplained, is plausible. A febrile spike in body temperature would be the first manifestation of the febrile seizure, and is supported by the near-death experience in the present case, MRI studies revealing a relationship between hippocampal structural anomalies [36], and recent video analysis [14]. Potential available remedies could include monitoring of body temperature for a sudden spike, and rectal diazepam could be available as an immediately applicable treatment until Emergency Medical Services arrived.

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Volume 8 Issue 3 March 2025

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